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Editorial

The Minute Blood Vessels in Disease

IT is now three centuries since the discovery of capillaries and since Harvey established their general function of giving continuity of blood flow in one direction from arteries to veins. Progress in understanding the role of minute vessels, arterioles, capillaries and venules in disease has been slow. For example, the small vessels of the diseased kidney have been the subject of interest since abnormal glomeruli were first described and still our understanding is fragmentary. We wish to point out a few encouraging examples of recent studies in this field and comment on their significance.

An important feature of several contributions is the utilization of technics which give three-dimensional visualization of small vessels. Friedenwald, in his study of small vessels of the human eye, obtained binocular vision in depth in fixed, cleared retinas and was still able to use a differential stain for capillary basement membrane. This technic made it possible to identify the capillary aneurysms of diabetic retinopathy, count them, and determine their place in the retinal vascular system.[1] Ashton improved this procedure by injecting the vessels with india ink which made possible a more exact differentiation between patent and thrombosed aneurysms. Identity and localization of hemorrhages was made possible by either technic. Ashton contributed the highly descriptive term, "dots and blots," for this distinctive form of retinal disease, referring to the appearance of the retina seen through the ophthalmoscope as "dots" for capillary aneurysms through which blood is flowing, and "blots" for localized hemorrhages.[2] The greatest interest to internists from these studies of retinal capillaries comes from Friedenwald's suggestion that there may be a kinship in pathogenesis of glomerular lesions in Kimmelstiel-Wilson syndrome and diabetic retinopathy with capillary aneurysms. Evidence is accumulating in support of this concept.[3] A line of study which began in pathologic anatomy of the eye is contributing towards a more accurate nosography of diabetes.

Orbison used the difficult and laborious method of model construction from serial sections in order to obtain a three-dimensional description of minute vessels in thrombotic thrombocytopenic purpura, and found aneurysmal dilatation at the arteriolar-capillary junctions. It appears that these aneurysms are easily seen in stained sections but had previously been erroneously identified as venules.[4] This beautiful study confirms and extends the interpretation made by Gore that abnormality of walls of small vessels precedes thrombosis in this puzzling disease.[5]

It may be pertinent to the question of localization of the aneurysms of Orbison that it was in this same high pressure segment of the vessel that Humble saw bleeding begin during the performance of the tourniquet test in patients with a wide variety of diseases.[6] The concept that small vessels have important specialized functions in hemostasis continues to be a profitable field for investigation.[7]

In their study of experimental scurvy with volunteers during World War II, workers in England used direct microscopic examination of the capillaries surrounding the hair follicles of the leg where the characteristic hemorrhages appear. They report that the first detectable vascular abnormality was the appearance of new capillaries looped about the keratotic follicles. These became dilated and erythrocytes appeared to pass through the capillary wall diffusely by diapedesis.[8]

Hartroft and Ridout used a number of standard histologic technics to reconstruct in three

dimensions, in its various stages, the growth and disappearance of the fatty cysts which are the most important hepatic lesions in rats with cirrhosis of choline deficiency.[9] Parenchymatous cells became overloaded with fat which was no longer distributed in fine particles but collected in large blobs which were then extruded from the cell. The fat of several adjoining cells, sometimes as many as sixty, was then contained in a fatty cyst, the wall of which was made of modified parenchymatous cells. As these cysts grow in size the minute blood and bile channels are compressed, pushed aside or torn, and eventually the cysts tend to rupture into either sinusoids or bile channels. According to these workers, not only are the walls of sinusoids injured by these fatty cysts but also when rupture is into the blood vascular channels the fat becomes a potential embolus to vessels in other organs. Sudden death of alcoholic persons with fatty liver is blamed on this mechanism by Durlacher and associates.[10]

A subject of debate for a long time is pathologic spasm as a cause of hypertensive encephalopathy. There has been a tendency in recent years to give a negative answer to the question of brain injury by this mechanism. The subject has been reopened by the publication of the brilliant experiments of Byrom who studied rats with experimentally produced renal hypertension, some of which manifested convulsions and other evidences of encephalopathy. He presents serial photographs made through skull windows of vessels on the surface of the cerebral cortex which show evidence of marked spasm during convulsive episodes, which had been absent before any attack and which disappeared with relief of hypertension. Using other suitable technics he develops a strong line of evidence that arterial spasm, focal ischemia and increased permeability of brain capillaries is responsible for encephalopathy in his animals. He suggests that the reaction of smooth muscle to stretching force described in 1902 by Bayliss is the cause of arterial constriction. His report should be studied in detail by all who are interested in hypertension.[11]

Lipid material released from an atheromatous ulcer may block small vessels, as indicated by the finding of clefts which have the size and shape of cholesterol crystals in sections of granulomatous or fibrotic lesions in viscera, and the demonstration of atheromatous ulcers in the artery supplying the part.[12] It seems that such a mechanism may sometimes be the crucial link between atheromata of the renal artery and the diffuse injury to one kidney which may cause malignant hypertension.[13] It is difficult to evaluate such a method of producing minute infarcts because the rarity with which this combination of findings is reported contrasts with the apparent abundance of opportunity for such accidents. Perhaps the distinctive microscopic evidence is not sought for as assiduously or systematically as is necessary, or possibly healing of the minute lesions commonly occurs. It is easy to imagine, perhaps erroneously, the occurrence of showers of minute emboli at intervals over a period of many years, eventually giving a picture of diffuse "degeneration" of an organ, and the failure to demonstrate cholesterol clefts at time of death.

Several constituents of blood may be responsible for occlusion of small vessels. Sickled erythrocytes in individuals without anemia seem especially adapted for this role. Recently, several reports have pointed out that individuals with the sickling trait, but without anemia, may under conditions not fully understood but commonly related to hypoxia, general anesthesia or surgical operations, become ill to a degree out of proportion to the precipitating cause, and may be found to have occlusion of important blood vessels.[14] The most fully described syndrome is splenic infarction associated with high altitude flying.[15,16] Obstruction of many capillaries by interlocked, packed sickled cells may lead to retrograde arterial obstruction with gross infarction of viscera.[17] Several pathologists in New Orleans have demonstrated to us a variety of gross lesions of this sort. When obstruction begins in brain capillaries death may occur before gross lesions appear, and brain sections show only capillaries packed with sickled cells and sometimes microscopic foci of necrosis.

When excessive quantities of thromboplastin enter the circulation, as from the placenta when this organ is prematurely separated, fibrinogen is converted into fibrin, which collects in clumps and blocks small vessels. Fibrinogen may disappear from the blood and hemorrhages result from failure of clotting as well as from fibrin emboli.[18,19]

Plasma globulins which become insoluble at low temperature, cryoglobulins, may occlude small vessels and cause cold weather purpura and even gangrene of digits.[20] Globulins with similar characteristics may possibly obstruct capillaries under conditions other than chilling, for

example, those of the glomeruli in experimental generalized Shwartzman's reaction.[21]

This fragmentary survey of progress in understanding what happens to small blood vessels in disease emphasizes some of the difficulties in demonstration of morbid anatomy. It is also apparent that current clinical methods of diagnosis have great limitations in this field. Minute vascular lesions, even if numerous, may give no clinical manifestations unless: (1) the vessels lie in an area of high visibility such as in the retina or skin where hemorrhages may be seen; (2) the injured tissue is unusually well supplied with pain receptors, as the joints seem to be; (3) small lesions give noticeable organ dysfunction, as in certain parts of the nervous system; or (4) injury gives highly useful laboratory findings such as microscopic hematuria.

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REFERENCES

1. FRIEDENWALD, J. S. A new approach to some problems of retinal vascular disease. *Tr. Am. Acad. Ophth.*, 53: 73–87, 1948.
2. ASHTON, N. Vascular changes in diabetes with particular reference to the retinal vessels. *Brit. J. Ophth.*, 33: 407, 1949. Injection of retinal vascular system in enucleated eye in diabetic retinopathy. *Brit. J. Ophth.*, 34: 38, 1950.
3. RIFKIN, H., LEITER, L. and BERKMAN, J. Diabetic glomerulosclerosis. American Lecture Series, 1952.
4. ORBISON, J. L. Morphology of thrombotic thrombocytopenic purpura with demonstration of aneurysms. *Am. J. Path.*, 28: 129–143, 1952.
5. GORE, I. Disseminated arteriolar and capillary platelet thrombosis. *Am. J. Path.*, 26: 155, 1950.
6. HUMBLE, J. G. The mechanism of petechial hemorrhage formation. *Blood*, 4: 69, 1949.
7. ZUCKER, H. D. Platelet thrombosis in human hemostasis: a histologic study of skin wounds in normal and purpuric individuals. *Blood*, 4: 631–645, 1949.
8. BARNES, A. E., BARTLEY, W., FRANKAU, I. M., HIGGINS, G. A., PEMBERTON, J., ROBERTS, G. L. and VICKERS, H. R. Vitamin C requirement of human adults. Medical Research Council Special Report Series No. 280, 28, 1953.
9. HARTROFT, W. S. and RIDOUT, J. H. Pathogenesis of the cirrhosis produced by choline deficiency—escape of lipid from fatty hepatic cysts into the biliary and vascular systems. *Am. J. Path.*, 27: 951–989, 1951.
10. DURLACHER, S. H., MEIER, J. R., FISHER, R., LOVITT, W. V., JR. Sudden death due to pulmonary fat embolism in persons with alcoholic fatty liver. *Am. J. Path.*, 30: 633–634, 1954.
11. BYROM, F. B. The pathogenesis of hypertensive encephalopathy and its relation to the malignant phase of hypertension. *Lancet*, 2: 201, 1954.
12. ZAK, F. G. and ELIAS, K. Embolization with material from atheromata. *Am. J. M. Sc.*, 218: 510–515, 1949.
13. HOWARD, J. E. et al. Hypertension resulting from unilateral renal vascular disease and its relief by nephrectomy. *Bull. Johns Hopkins Hosp.*, 94: 51–85, 1954.
14. BAUER, J. and FISHER, L. J. Sickle cell disease—with special regard to its nonanemic variety. *Arch. Surg.*, 47: 553–563, 1943.
15. CONN, H. O. Sickle cell trait and splenic infarction associated with high-altitude flying. *New England J. Med.*, 251: 417–420, 1954.
16. COOLEY, J. C., PETERSON, W. L., ENGEL, C. E. and JERNIGAN, J. P. Clinical triad of massive splenic infarction, sicklemia trait, and high altitude flying. *J. A. M. A.*, 154: 111–113, 1954.
17. THOMPSON, R. K., WAGNER, J. A. and MACLEOD, C. M. Sickle cell disease—report of a case with cerebral manifestations in the absence of anemia. *Ann. Int. Med.*, 29: 921–927, 1948.
18. SCHNEIDER, C. L. Thromboplastin complications of pregnancy. *Bull. Margaret Hague Maternity Hosp.*, 4: 2–15, 1950–1952.
19. WEBER, L. L., MERANZE, D. R. and KAPLAN, F. Intravascular clotting complications of pregnancy. *Am. J. Obst. and Gynec.*, 64: 1037–1048, 1952.
20. LERNER, A. B. and WATSON, C. J. Unusual purpura associated with the presence of a high concentration of cryoglobulin. *Am. J. M. Sc.*, 214: 410–415, 1947.
21. THOMAS, L., SMITH, R. T. and VONKORFF, R. Cold precipitation by heparin of a protein in rabbit and human plasma. *Proc. Soc. Exper. Biol. & Med.*, 86: 813–818, 1954.

Clinical Studies

Post-traumatic Renal Insufficiency in Military Casualties*

I. Clinical Characteristics

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POST-TRAUMATIC renal insufficiency is a major problem in military medicine. In World War II 40 per cent of one group of severely wounded patients developed acute post-traumatic renal insufficiency with a case fatality rate of 90 per cent among the severely oliguric.[1] Renal lesions were found in 18.6 per cent of 427 unselected battle casualties who died in Army hospitals.[2] Among 165 autopsied Korean battle casualties pathologic evidence of renal damage occurred in 39 per cent and clinical uremia was severe enough to account for death in 14 per cent of the cases.[3]

The renal lesion in acute renal failure of traumatic and other origin has been studied by several investigators[2,4–6] and the underlying similarity in the lesions emphasized by Lucké.[4] The definitive description and the concept of pathogenesis has been further clarified by the work of Oliver.[7] A unified concept of acute renal failure as a clinical and biochemical sequel of several diseases has been documented by Swan and Merrill.[8]

The type of injury to the kidney and the subsequent clinical and biochemical changes in the renal insufficiency of military casualties are not qualitatively different from those seen in civilian medicine; but special consideration of the former seems warranted because: (1) Development of clinical uremia and potassium intoxication is accelerated in this group of patients, with a resulting excessively high case fatality rate; (2) this rapid course presents special therapeutic problems in which use of the artificial kidney requires evaluation; (3) occasional civilian patients injured in accidents, or after extensive surgery, develop renal failure with these characteristics,[9] and (4) there is a clear possibility, in the event of war, of widespread casualties among civilians who may be expected to follow a similar course and to present similar problems.

The experience presented here includes all patients, fifty-one in number, who developed post-traumatic renal insufficiency and were admitted to a Renal Insufficiency Center† in Korea during 1952. This represents most of the combat casualties who developed oliguria, as defined subsequently, and who survived the first forty-eight hours of resuscitation and surgery; patients who developed overt transfusion reactions were excluded from this group. The Center was equipped with a trained staff, an adequate supporting laboratory, and a Brigham-Kolff type artificial kidney. Ten additional patients were treated in a detailed, preliminary survey by members of the staff before the artificial kidney was available or a permanent location for the Center established. The experience presented here constituted a

† Operated jointly by the Surgical Research Team, AMSGS, Washington, D. C., and personnel of the Eighth Army, Korea.

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unique opportunity to evaluate the usefulness of a center for the treatment of this group of patients in the forward chain of casualty evacuation.

DEFINITIONS AND METHODS

By *post-traumatic renal insufficiency* is meant impairment in renal function secondary to diffuse parenchymal renal damage[7] following trauma to the patient. Manifestations of post-traumatic renal insufficiency include the characteristic urinary, chemical and clinical findings in patients with acute renal failure of any origin. These findings are superimposed upon the expected sequelae of the antecedent wound, from which they cannot always be clearly differentiated.

Oliguria is arbitrarily defined as a urine output of less than 500 ml. in twenty-four hours. This is based on the demonstration that 500 ml. approximates the lowest sufficient volume of urine to clear the plasma of a normal metabolite load at normal maximal renal concentrating ability.[10] Of course, with impairment of concentrating ability high levels of azotemia may occur at much higher rates of urine formation.

Diuresis is defined as beginning when a twenty-four-hour urine volume equals or exceeds 1 L. after a preceding period of oliguria. During the recovery phase the level of azotemia is seldom lowered by a urine volume of less than 1 L.*

The twenty-four-hour urine collections were taken by constant drainage from an inlying Foley catheter. Blood for chemical determinations was drawn with minimal stasis into previously heparinized syringes, centrifuged promptly and the plasma analyzed (by the following methods) for non-protein nitrogen,[11] carbon dioxide combining power[12] and chloride.[13] Sodium and potassium were measured in diluted, heparinized plasma by means of a Baird-Associates flame photometer using an internal lithium standard.

Electrocardiograms were taken with a direct-writing Sanborn electrocardiograph using standard and unipolar limb leads and precordial leads V_1 through V_6.

* In contrast to the finding of Swan and Merrill,[8] twenty-four-hour urine volumes in these patients did not usually increase at noticeably different rates below and above a 400 ml. daily output level; however, typical diuresis uniformly followed daily urinary outputs of 750 to 1,000 ml.

DIAGNOSIS AND INCIDENCE

The incidence of post-traumatic renal insufficiency, as so defined, could be determined only by the routine use of sensitive diagnostic renal function tests on a large random sample of wounded men. Unfortunately such a study has not been carried out. The diagnostic criterion used at the forward hospitals as a basis for referring patients to the Renal Insufficiency Center was that of oliguria (less than 500 ml./24 hours) without hypotension on the second or third post-wound day. The presence of uncomplicated dehydration as a cause of oliguria was excluded by a urinary specific gravity of less than 1.030 (it was usually below 1.020). Diagnosis was occasionally substantiated by lack of diuresis in response to a water-load test, such as the infusion of 1,000 ml. 5 per cent dextrose in water intravenously in one hour. These simple criteria indicated the patients' need for specialized therapy and doubtless excluded many cases of milder renal damage.* Because potassium intoxication and clinical uremia developed rapidly in the oliguric patients, they were evacuated to the Center as soon as the diagnosis was made.

During the last six months of 1952 there is reason to believe that almost all combat casualties who developed oliguria and who survived forty-eight hours after surgery were referred to the Renal Insufficiency Center. During this period forty-two patients were referred to the Center from among approximately 8,000 wounded or injured in action cases admitted to medical treatment facilities.[14] This represents an incidence of about 0.5 per cent or one oliguric patient per 200 surviving casualties. In a group of 4,000 consecutive acutely wounded patients treated at one forward hospital (1952–1953) nineteen patients developed oliguria, an incidence also approximating 0.5 per cent.

Post-traumatic renal insufficiency therefore is a statistically minor complication of wounding. This is not a cogent indication of its importance in military medicine however. Approximately 20 per cent of soldiers hit in action in Korea were killed instantly or died before they reached forward hospitals.[14] Of the casualties who reached the forward hospitals alive, approximately 97 to 98 per cent survived their wounds.

* As will be emphasized subsequently, it is possible that renal insufficiency without oliguria might represent more of a therapeutic problem in an older casualty population but this was rarely the case in these military casualties whose average age was 22.7 years.

Most of these had relatively minor wounds with uncomplicated convalescence. It is in the smaller number of severely wounded that renal failure constitutes an important cause of death during the postoperative period. In Italy during World War II at least 40 per cent of a group of very severely wounded casualties* studied at one forward hospital developed acute renal failure. Uremia was thought to be the major cause of death, accounting for 54 per cent of all fatalities in this group and resulting in an over-all mortality among severely wounded of 19 per cent.[1]

In Korea prompt evacuation made possible the early treatment of casualties with massive injuries. Forty-three such casualties who lived three days or longer after receiving fifteen or more pints of blood on the day of injury were studied by the Surgical Research Team. Twenty-one per cent of this group developed oliguria and an additional 14 per cent developed azotemia and clinically evident uremia while maintaining a daily urinary output of more than 500 ml.[15] It is this range of incidence which indicates the real importance of post-traumatic renal insufficiency as a military medical problem.

It may be anticipated that the incidence of post-traumatic renal insufficiency will vary in different military situations, depending on the availability of blood and the rapidity with which casualties are evacuated. Hence the data from Korea may represent a minimum incidence with present methods of evacuation, resuscitation and surgery.

ETIOLOGY

Extensive studies on the effects of shock[1,16–21] and of hemoglobin[22–27] on renal function in man, and attempts to produce acute renal failure in experimental animals,[28–31] have not completely elucidated the relative roles of renal ischemia and of blood or tissue pigments in the pathogenesis of the renal tubular damage.

* Non-transportable injured. In the subsequent discussion it is recognized that there is no completely satisfactory, objective definition of the term *severely wounded* as employed here. Because of improved technics of evacuation and medical care in the forward areas more extensive wounds became compatible with survival. In general, the "severely wounded" were those patients whose immediate survival in the judgment of physicians in the forward areas, *depended* on prompt evacuation, resuscitation and surgery. In such patients large volumes of injured tissue were regularly found and hypotension responded only to massive transfusions.

Although it was realized that little could be added to the basic information about pathogenesis in such an uncontrolled clinical study, an attempt was made to evaluate some of the antecedent and possibly etiologic factors in this group of patients. It was hoped that a pattern might emerge by which the occurrence of post-traumatic renal insufficiency in an individual patient could be predicted.

Evacuation Time. As a general rule the acutely wounded patient is carried by litter from the point of wounding to the aid station supporting his battalion. Preliminary first aid treatment is given. Severely wounded patients are then evacuated to a forward surgical hospital by helicopter during the day and by ambulance at night. Less severely wounded patients travel by litter-jeep or ambulance through regimental collecting and division clearing stations and for definitive surgery if necessary at the forward surgical hospital. Albumin, dextran and whole blood are given as indicated along the route of casualty evacuation, and entries are made on the field medical record. Subsequent data have been obtained from these entries.

The time required for this evacuation sequence from time of wounding to forward hospital admission averaged 4.6 hours (range, one to eleven hours) in fifty-one patients whose records permitted this calculation. Approximately half of the patients reached a forward hospital within three hours of the time of wounding. The average time of evacuation in a control group of forty-one severely wounded patients who did not develop renal insufficiency was 3.5 hours. It can be concluded that the delay in resuscitation necessitated by evacuation *per se* did not lead to the development of post-traumatic renal insufficiency.

Duration and Severity of Hypotension. (Systolic arterial blood pressure of less than 100 mm. Hg.) In fifty patients from whose records estimates could be made the duration of hypotension averaged 7.3 hours (range, two to twenty-six hours). Over half of the patients were hypotensive for six hours or less but no patient in this group was hypotensive for less than two hours. The mean duration of hypotension is considerably longer than the average evacuation time. This reflects the fact that persistent hypotension frequently prolonged preoperative resuscitative efforts, or recurred during or following operation.

Serial blood pressure readings were not available on any patient (and single readings only on

six) prior to admission to the forward surgical hospital, so that any estimate of the total duration of arterial hypotension is necessarily crude. These estimates include the evacuation time when the patient was hypotensive on hospital entry, unless normal blood pressures were previously recorded.

The estimated duration of hypotension in a control group of forty-one severely wounded patients who did not develop oliguria was approximately six hours. It can be concluded that hypotension alone cannot be incriminated as a cause of renal failure. The amount of volume replacement therapy administered at the forward surgical hospital and during the prior evacuation period constitute a further general measure of the degree of hypotension.

All sixty-one patients* received whole blood (and occasionally albumin, plasma or dextran) during the immediate post-wound period. Total volume therapy averaged 5.9 L. per patient (range, 0.5 to 15.5 L.). Whole blood accounted for 95.3 per cent of the total volume therapy given with the remainder divided among plasma 2.4 per cent, albumin 1.8 per cent and dextran 0.5 per cent. This approximated the relative use of these various oncotic agents in all the wounded at the time of this study. The resuscitative use of volume therapy was distributed in time as follows:

During evacuation to hospital	11%
Before surgery at hospital	30%
During surgery at hospital	40%
Postoperative period	12%
Unable to assign	7%

This distribution of volume replacement gives only a fair index of the presence and severity of hypotension, however, because (1) during evacuation blood was not always readily available and was difficult to administer, and (2) many of the most severely wounded patients were operated upon before their blood pressures were restored to normal.

In the group of forty-one severely wounded patients who did not develop post-traumatic renal insufficiency, each received an average of 12 L. of volume therapy, largely as whole blood, during the total period of resuscitation (first twenty-four hours after wounding). It is possible that the more liberal use of whole blood may have protected these patients against more severe renal damage.

* See introductory remarks.

Hemolysis and Plasma Hemoglobin. Type O whole blood was used exclusively in these patients. No overt transfusion reactions occurred. If increased but subclinical hemolysis of the recipients' erythrocytes by the hemagglutinins of the transfused blood contributed to the pathogenesis of the renal damage, it would be anticipated that fewer patients with type O blood would be found in this series than the relative incidence of type O in the population as a whole. Table 1 lists the blood types in the present series and a random sample of Occidental individuals; the differences are not statistically significant. This agrees with a similar study carried out by the Board for the Study of the Severely Wounded in World War II.[1]

TABLE 1
INCIDENCE OF BLOOD TYPES IN PATIENTS WITH ACUTE POST-TRAUMATIC RENAL INSUFFICIENCY

Agglutinogen	No. of Patients	Per cent	Per cent of Normal Population*
O	23	55	41.8
A	12	29	37.7
B	5	12	13.9
AB	2	5	6.6

* From SUNDERMAN and BOERNER. Normal Values in Clinical Medicine, p. 74. Philadelphia, 1949. W. B. Saunders Company.

Because of the long supply route from the United States, whole blood was used in the forward areas in Korea seven to twenty-eight days (average of about two weeks) after its withdrawal from the donor. Figure 1 illustrates the relationship between the age of blood and its plasma hemoglobin level.[32,33] Thus a patient receiving 6 L. of two week old blood receives an infusion of about 2 gm. of hemoglobin at a time when there is probably marked renal vasoconstriction. In a study of renal function in casualties in Korea, however, Ladd[16] could find no correlation between the plasma hemoglobin concentration and the degree of impairment of inulin and PAH clearances. He also found similar reduction in clearance in two patients resuscitated with dextran alone and in one patient resuscitated with fresh type-specific, compatible whole blood. The plasma hemoglobin concentrations and total amount infused are low in comparison with amounts producing renal vasoconstriction in man.[24,25] Myoglobin may

have been implicated in patients with massive tissue destruction or with severe, prolonged shock.[1]

Severity and Location of Wound. Post-traumatic renal insufficiency tended to occur as a complication in the most severely wounded, as population or with the group dying after initial hospital care is striking. Duration of hypotension and volume of whole blood given were also generally greater in patients with wounds of the trunk. Of interest also is the high incidence of wounds of the kidney usually resulting in

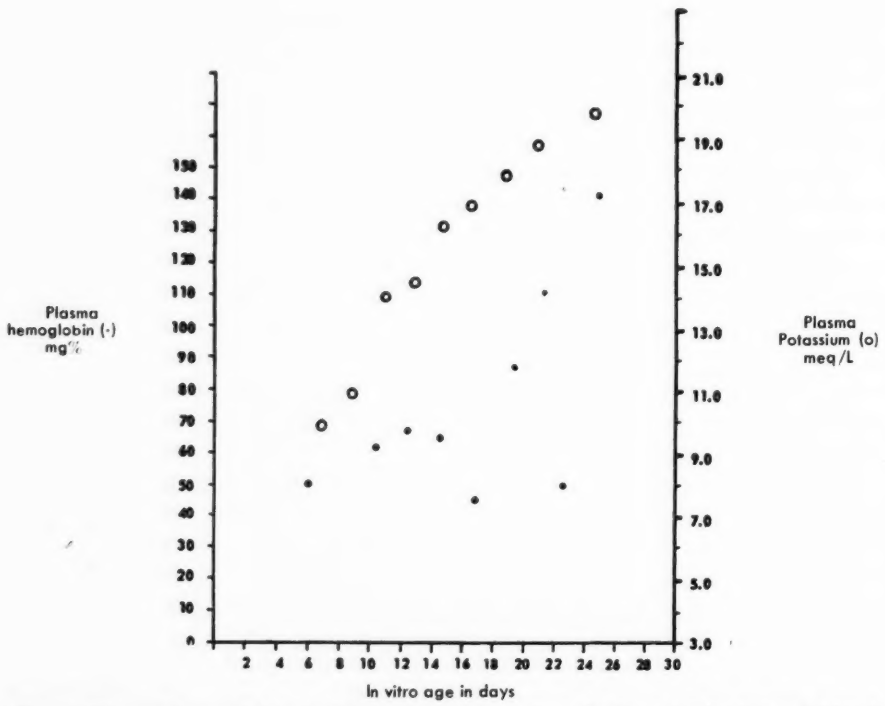

FIG. 1. Plasma hemoglobin (solid dots) and potassium (hollow dots) of stored blood in relation to age. Values are means of at least ten samples except for those on day 7 (five samples) and day 9 (two samples). Plasma was obtained from bottles later used for resuscitation at a forward surgical hospital.

might be anticipated from what is known of the pathogenesis of the condition and from the amount of volume replacement (5.9 L. per patient) needed for resuscitation. Ladd found that the renal blood flow and filtration rate were in general depressed in direct relation to the severity of the wound, as graded by an arbitrary point system for estimating the extent of the physiologic impact including volume replacement required and amount of tissue damage.[16]

Table II lists the location of wounds encountered in the present series of patients compared with similar data obtained during World War II[1] and in previous combat experience.[14,34] Both perforating and penetrating wounds occurred in all groups.

The higher incidence of thoracoabdominal and abdominal wounds in patients developing renal failure compared with the general casualty nephrectomy. None of the patients sustained bilateral renal trauma, however.

In summary, prolonged periods of hypotension, infusion of necessarily large volumes of relatively old whole blood, and the severity of the initiating wounds are possible factors in the etiology of post-traumatic renal insufficiency, implicated by their uniform occurrence in the oliguric patients referred to the Renal Insufficiency Center. There were a number of casualties, however, who failed to develop oliguria despite apparently identical histories and similarly severe wounds and prolonged periods of hypotension.

Likewise the occurrence of acute post-traumatic renal insufficiency could not be *predicted* on the basis of the foregoing data. However, such prediction with an accuracy of about 33 per cent[15] was possible by observing the response of low postoperative blood pressures

to whole blood transfusion. Many of the patients might well have died in shock without energetic and sustained resuscitative care in the postoperative interval. Patients who did not develop oliguria usually experienced a prompt blood pressure response to small transfusions.

Clearance studies of renal function indicate that there is probably some measurable damage to the kidneys in almost all casualties who are severely wounded and undergo a period of hypotension.[1,16] It is not clear whether such patients develop the same type or severity of

TABLE II

NUMBER OF WOUNDS OF SELECTED SITES PER 100 CASUALTIES WITH WOUNDS OF ANY SITE: GENERAL CASUALTY POPULATION COMPARED WITH PATIENTS WITH POST-TRAUMATIC RENAL INSUFFICIENCY

Site of Wound	Korean Conflict*		Patients with Renal Failure	
	All Wounded in Action Admissions†	Patients Dying of Wounds†	Present Series (61 patients)	World War II (78 patients)‡
Head, face, neck, extremities, with and without fracture	145	98	50	50
Abdomen§	13	33	59	35
Chest	13	27	..	22
Thoracoabdominal	1	6	26	14
Liver	1	4	21	19
Kidney	1	3	23	17
Spinal cord and vertebrae	2	4	2	1
Crush	NA‖	NA‖	5	6

* Based on preliminary unpublished data compiled from tabulations of individual medical records on all battle wound and battle injury admissions to medical treatment facilities in 1950–1952. Data obtained from Medical Statistics Division, Office of The Surgeon General, Department of the Army.[14]

† Data for wounded in action (WIA) admissions include data for patients dying of wounds (DOW).

‡ Studied by Board for the Study of the Severely Wounded.[1]

§ Includes pelvis and excludes liver and kidney.

‖ Not applicable (NA) to data for all WIA and DOW, all of which have been tabulated according to anatomic site, including those whose diagnosis was "crushing."

This experience indicated that acute renal failure impended in the postoperative period when an excessively large volume of blood was required to correct hypotension, in the absence of continuing hemorrhage.

RENAL INSUFFICIENCY WITHOUT OLIGURIA

Table III presents eight patients who had marked impairment of renal function but who were never or only transiently oliguric. Renal insufficiency without oliguria probably occurred much more frequently than indicated here, but with absent or undiscovered oliguria and without obvious clinical uremia such patients passed through the regular chain of evacuation. Potassium intoxication was usually not a serious problem in this group of patients.*

morphologic renal lesion as that seen in the oliguric patients. The smooth frequency distribution of the duration of oliguria in surviving patients suggests that at least the functional renal lesion in oliguric patients differs only in degree of severity rather than qualitatively from that in non-oliguric patients. (Fig. 2.) The characteristic peak expected on days 9 to 11 is not seen although it might have been found had a larger number of patients survived long enough for diuresis to begin.

The occurrence of (1) renal damage demonstrated by relatively sensitive clearance technics, (2) marked azotemia and occasionally clinical uremia without oliguria or with very transient oliguria and (3) overt oliguria of varying dura-

* Patient 17 had severe hyponatremia (serum Na, 117 mEq./L.) on admission to the Renal Insufficiency Center. A concurrent potassium level of 7.3 mEq./L. was associated with marked electrocardiographic findings of potassium intoxication. Dialysis was performed at once. Further inquiry revealed renal disease in the past in which his physician recommended his taking added salt. Persistent hyponatremia required such therapy during the diuretic phase.

tion among severely wounded casualties who have sustained a period of hypotension suggests that there is a regular gradation of renal damage following wounding. Attention has been largely directed toward the most marked degree of renal damage manifested by oliguria because it alone appears to require specialized treatment.

TABLE III

PATIENTS WITH EVIDENCE OF RENAL FAILURE WITHOUT OLIGURIA

Patient No.	Type of Wound	Evacuation Time (hr.)	Duration of Hypotension (hr.)	Volume of Colloid Therapy (L.)	Maximum NPN (BUN) Concentration (mg. % on PWD*)		Minimum Urine Volume (ml. on PWD)		PWD of Diuresis
17	Bilateral blast amputation of legs with extensive infection; superficial wounds; laceration of femoral vein	3.0	5.0	14.3	219	8	1050	2	..
24	Lacerations, inf. vena cava; 2 perforations of duodenum	3.5	4.0	12.0	235†	6	915	3	..
31	Perforations, hepatic and splenic flexures of colon; laceration of inf. vena cava; bruise of duodenum	2.5	3.0	8.7	109‡	2	500	1	2
52	Perforations, right and left lobes of liver, ascending colon, duodenum and stomach	?	?	3.5	321	6	1000	1	..
A	Bilateral traumatic amputation of legs at mid-calf, with many metal and bone fragments	2	8	9.5	(130)	5	1100	1	..
B	Perforated colon	8	8	1.0	100	4	800	4	..
C	Extensive lacerations of scalp, face, arms, left leg and back; multiple perforations of small bowel; fractures of both humeri	3	4	13.3	85	4	1200	1	..
D	Perforations of kidney, spleen, lumbar spinal canal with lower extremity diplegia	4	?	4.3	210	5	750	1	..

Patients 17, 24, 31, 52 from the series reported here. Patients A–D selected from experience at a forward surgical hospital.[15]

* Post-wound day.

† On PWD 3: CIn 2 ml./min.; CPAH 10 ml./min. On PWD 7: urine volume was 3600 ml., CIn 22 ml./min.; CPAH 131 ml./min.; TmPAH 27.6 mg./min.

‡ On PWD 3: urine volume was 1540 ml., CIn 41; CPAH 208 ml./min.; TmPAH 30 mg./min.

POTASSIUM INTOXICATION

The frequency and rapidity of potassium intoxication constitute the most important difference between the post-traumatic renal insufficiency of combat casualties and the acute renal failure usually seen in civilian practice.

Myocardial potassium intoxication occurs in the presence of hyperkalemia but its severity is not strictly correlated with the plasma potassium concentration. Potentiated by concurrent hyponatremia, hypocalcemia and possibly other factors, its actual myocardial effect and the imminence or remoteness of fatal cardiac arrest are accurately reflected in the electrocardiogram.[35–41]

Figure 3 compares the first recorded plasma potassium concentration, corresponding to the day of admission to the Renal Insufficiency Center, with the theoretically expected value in the non-traumatized "normal" as calculated by Strauss.[42] Nine plasma potassium values fell within normal or expected limits; the low value in one of these patients may be explained by severe metabolic alkalosis due to unreplaced gastrointestinal fluid losses. Elevated initial plasma potassium concentrations were recorded in all but six of fifty-one oliguric patients and in six of eight "non-oliguric" patients. In one patient a plasma potassium value of 7.5 mEq./L. was noted on the *first* post-wound day, and concentrations exceeding 7.0 mEq./L. occurred in one-third of the patients within the first four days of wounding. Death from cardiac arrest secondary to potassium intoxication occurred not infrequently as early as the fourth day after injury prior to the use of the artificial kidney. All patients demonstrated electrocardiographic evidence of myocardial intoxication sometime during the course of oliguria persisting longer than five days.

In twenty patients with adequate records, the mean increment of plasma potassium concentration *following the initial value* (obtained on admission) was 0.7 mEq./L. per twenty-four hours, over twice the theoretical rate.[42] The average patient may therefore accumulate lethal concentrations of plasma potassium (9.0 mEq./L. or above) within six days of wounding, well before significant diuresis may be expected. Because of frequent hemodialyses, supervening diuresis, use of cation exchange resins for potassium removal and gastrointestinal losses of potassium, increments in plasma potassium concentrations following the initial values rarely reflect the true rate of catabolic potassium

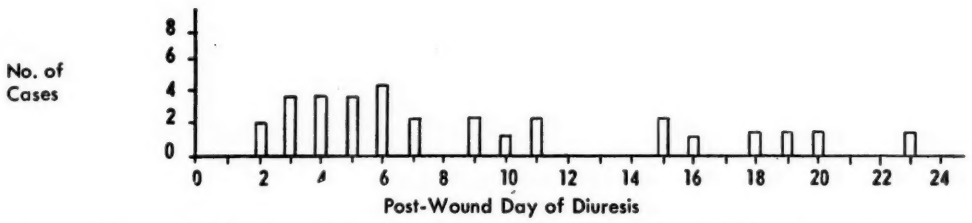

FIG. 2. Post-wound day on which urine volume exceeded 1,000 ml./24 hours in twenty-nine surviving patients with post-traumatic renal insufficiency.

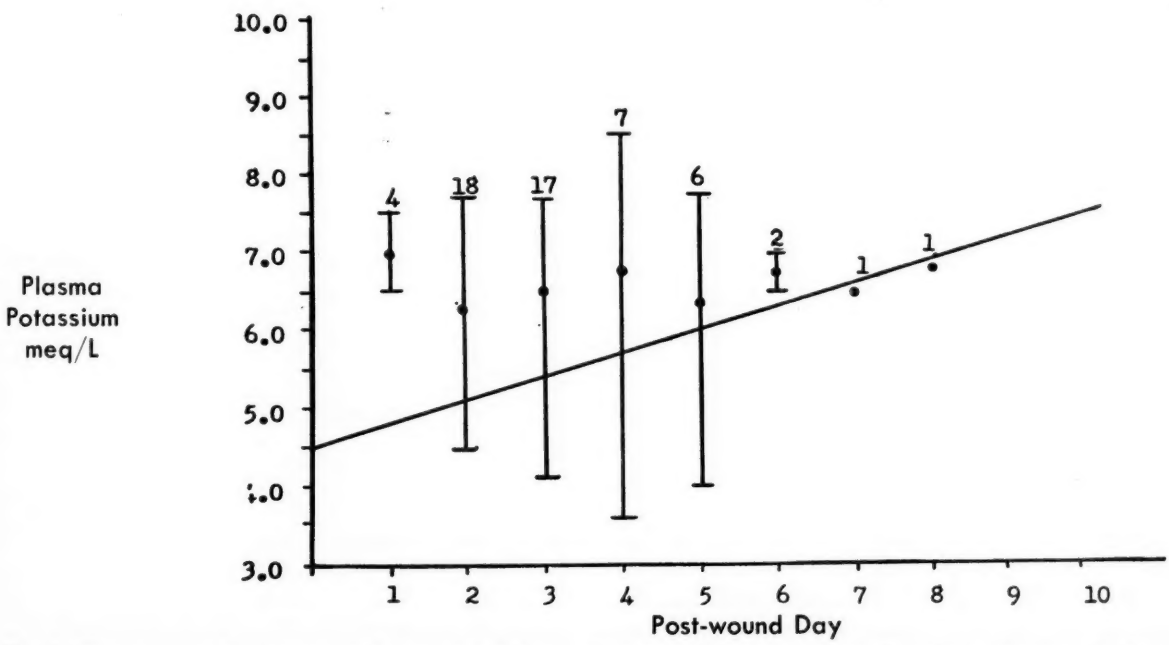

FIG. 3. Plasma potassium concentrations on admission to Renal Insufficiency Center. Average and range of values given for the number of patients indicated in each group. Diagonal represents theoretic accumulation of 0.3 mEq./L./24 hours.

liberation, but rather afford a *minimum* estimate of it.

Case 1 was studied before the artificial kidney was available in Korea and illustrates the practical clinical problem:

A twenty year old infantryman received multiple shell fragment wounds of his left arm with a severed brachial artery and damage to his median and ulnar nerves. Débridement and direct anastomosis of the brachial artery were performed four and one-half hours later at a forward surgical hospital. Although admission blood pressure at the surgical hospital was 140/80 and pulse was 104, systolic blood pressure soon dropped below 100 mm. Hg where it remained for twelve hours before, during and after surgery despite infusion of 8 L. of whole blood. Postoperatively the patient's skin remained warm, dry and vasodilated. Thirty-seven hours later blood pressure reached 110/70 where it remained. The left arm appeared nonviable. On the fourth post-wound day, clinical uremia appeared with stertorous breathing and stupor, he bled from nose and gums, mild cyanosis appeared and he expired quietly. Pertinent data are summarized in Table IV.

TABLE IV
DATA IN CASE 1

Post-wound Day and Time (hr.)		Urine Volume (ml.)	Plasma			Treatment
			NPN (mg. %)	K (mEq./L.)	ECG	
1	0600	68	73.8	4.3	.....	1,000 ml. 5% D/W
2	0600	79	158	7.5	Moderate K intoxication	1,500 ml. 5% D/W
3	0600	100	220	8.0	.....	40 gm. cation exchange resin;* 1,000 ml. 5% D/W
4	0100	179	232	8.6	.....	.....
	0800	...	272	8.7	Severe K intoxication	40 gm. cation exchange resin
	1920	...	277	11.2	.....	Oxygen

* All resin used was the carboxylic exchanger SKF No. 648, furnished by Smith, Kline and French Laboratories.

Death on the fourth post-wound day in cardiorespiratory failure is believed to have been due to potassium intoxication.

There are three general reasons why potassium intoxication may occur so frequently and progress so rapidly in this group of patients:

1. *The breakdown of infused erythrocytes:* Erythrocytes contain approximately 100 mEq. of potassium per L. of cells. Figure 1 illustrates the rise of potassium concentrations in the plasma of stored blood prior to infusion into casualties in Korea.[32] The average patient in this series receiving 5.9 L. of fifteen day old blood during resuscitation receives 50 mEq. of potassium in the infused plasma. Following transfusion about 10 per cent of infused red cells disappear from the circulation within the first few hours, with consequent liberation of about 30 mEq. of potassium. Destruction of infused red cells is accelerated in the severely wounded for several days following wounding as evidenced by falling hematocrits, slight elevations of serum bilirubin and studies of red cell survival.[33]

However, an infusion of 80 to 100 mEq. of potassium may not be expected to raise plasma levels significantly since it is distributed in an exchangeable body pool of about 3,300 mEq. in a normal 70 kg. subject.[43] The potassium of infused plasma and that derived from erythrocytes of diminished viability do not produce significant hyperkalemia. This is demonstrated by eight patients who received between 6.5 and 24 L. of whole blood during resuscitation.[44] The mean plasma potassium on admission to a forward surgical hospital was 4.4 mEq./L. (range, 3.5 to 5.4); following resuscitation and surgery the mean level was 4.8 mEq./L. (range, 3.0 to 6.2).

2. *The breakdown of tissue cells:* Potassium is contained primarily in muscle cells in a concentration of nearly 160 mEq./L. of cell water. Potassium is released from this reservoir in the wounded man by destruction of tissue at the site of initial injury, in the course of secondary infection, and because of ischemia and necrosis secondary to injury of nutrient blood vessels.

Tissue catabolism is accelerated by the stress of wounding and surgery, fever, starvation and the immobility imposed by bedrest, casts and painful wounds. The rate of potassium release apparently varies widely according to the nature of the wound and the amount of ischemia and infection. In a number of cases progression of hyperkalemia seemed to be blunted by removal of a gangrenous extremity or a second débridement of a dirty wound.[45]

3. *Electrolyte shifts:* Especially in the presence of acidosis, movement of potassium ions from the intracellular to the extracellular fluid may further contribute to the rising plasma potassium concentration.[8,37]

Despite the large excretory load of potassium in patients with varying degrees of post-traumatic renal insufficiency, usually only those patients who were actually oliguric developed dangerous hyperkalemia. This reflects the remarkable ability of the kidney to excrete potassium even when diseased.[46]

CLINICAL MANIFESTATIONS

The progressive clinical, biochemical and electrocardiographic abnormalities following acute urinary suppression and their prompt resolution with diuresis are now well recognized and will not be recounted here.[8,37,42] In acute renal failure following wounding this basic pattern is altered in the following important respects: (1) rates of clinical and chemical change, (2) prominent malnutrition, loss of body weight, rapid edema accumulation, (3) severe infection, (4) impaired wound healing, (5) bleeding tendency and anemia and (6) the incidence of hypertension.

Rates of Clinical and Chemical Change. Clinical uremia: Anorexia, nausea, vomiting, lethargy and drowsiness attributable to uremia appeared in two-thirds of these patients by the fifth post-wound day and, as evidenced by clinical improvement following hemodialysis, as early as the second day. In several patients without intervening dialysis or diuresis, lethargy soon progressed to disorientation and coma, and death usually occurred approximately six days following wounding.[47]

Many manifestations of clinical uremia could often be attributed rather to the expected effects of severe sepsis, extensive wounds, reparative surgery of the chest or gastrointestinal tract, and persistent or recurrent hypotension. However, uremic symptoms usually developed in patients without such severe intercurrent processes when NPN concentrations exceeded 200 to 250 mg. per cent in the absence of diuresis.* Since these levels usually occurred by the fifth post-wound day uremia was thought also to contribute to the clinical picture in most instances, in addition to the other factors.

The clinical behavior of these patients contrasts sharply with that in cases of acute renal failure of non-traumatic origin in which uremic symptoms may appear by the sixth or seventh day and remain mild throughout the entire course.[8]

Azotemia: Figure 4 compares the first recorded plasma NPN concentrations, corresponding to the day of admission to the Renal Insufficiency Center, in each of fifty-two patients with the theoretically expected value.[42] Initial values are uniformly higher than the theoretical figure. *Following the initial value*, the mean rate of plasma NPN accumulation in the entire series is 50 mg. per cent per twenty-four hours, four times the rate calculated by Strauss.[42] This may occur despite the therapeutic regimen described in the companion paper.[47]

The accelerated accumulation of NPN is a measure of the accelerated catabolism which characterizes these patients and corresponds to rates of clinical progression and of developing hyperkalemia and potassium intoxication.

Hyperkalemia has been discussed previously.

Malnutrition, Loss of Body Weight, Rapid Edema Accumulation. Marked wasting of both muscle and subcutaneous fat was noted in patients surviving longer than seven to ten days. Adequate body weight measurements not affected by changes of casts, interval amputations and large débridements are available in sixteen patients. The mean body weight loss was 1 kg. per day (range, 0.5 to 1.6), the clinical degree of hydration remaining approximately constant. Patients lost between 10 and 30 per cent of their admission weights during an average course of eleven days (range, 4 to 33 days). Marked fluid restriction had been enforced in these patients and weight loss was not usually more rapid during diuresis.

Parenteral caloric intake varied between 100 and 1,000 calories per twenty-four hours. Oral

* Onset of diuresis was usually associated with marked clinical improvement although NPN levels continued to rise. One patient was clinically well with a massive diuresis (5 to 8 L. of urine/day) for six consecutive days during which NPN exceeded 300 mg. per cent.

or intragastric intake was only rarely possible but permitted 1,000 to 2,500 calories per twenty-four hours during the oliguric phase. All caloric intake was sharply curtailed by necessary volume restriction, ileus or direct injury to the gastrointestinal tract. Caloric intake was thought to be insufficient in all instances despite vigorous efforts to increase it.

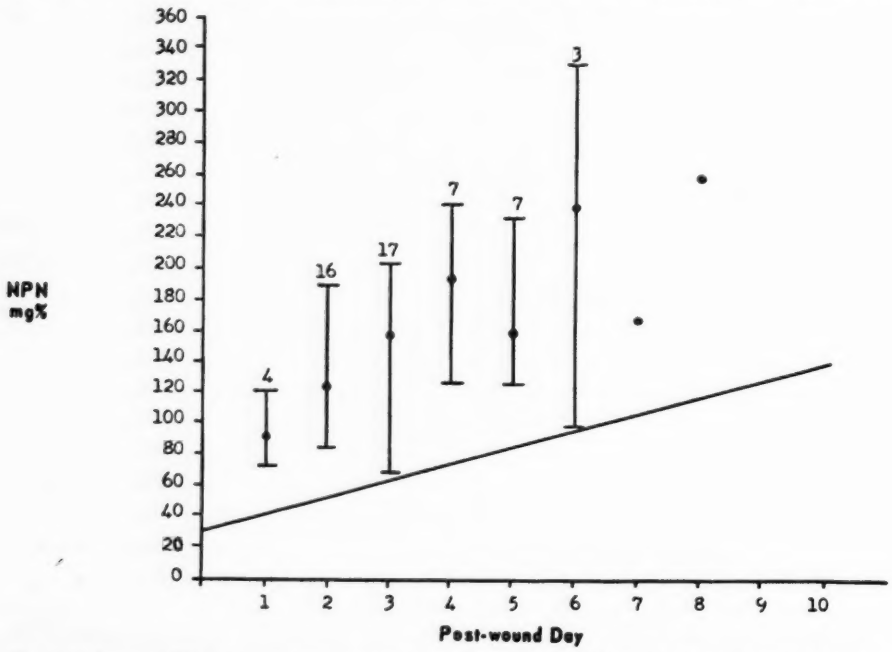

FIG. 4. Plasma NPN concentrations on admission to Renal Insufficiency Center. Average and range of values given for the number of patients indicated in each group. Diagonal represents theoretic accumulation of 12 mg. %/24 hours.[42]

Accelerated catabolism was demonstrated in several striking instances when peripheral edema developed in the presence of positive non-colloid fluid balances not exceeding 400 ml./day. It was thought that, relative to tissue mass, the body water pool gained volume at a rate exceeding the combined rates of insensible perspiration, sweat and other fluid losses. With restricted intake, such increments in volume could arise only from the preformed water and water of oxidation of the catabolized tissue, with a small contribution from the infused glucose. It is concluded that conventional replacement allowances (measured water losses plus 750 to 1,000 ml./day) are excessive for patients with post-traumatic renal insufficiency. In any event, fluid balance should be adjusted on clinical grounds, not made to approximate a fixed, empiric value.

Severe Infection. Penicillin and streptomycin were routinely given beginning on the day of injury. Broad-spectrum antibiotics were usually substituted within five days in most patients. Despite liberal use of antibiotics in patients whose renal antibiotic excretion was undoubtedly impaired, fever, leukocytosis, pulmonary and/or wound infection regularly occurred as is shown in Table v. Whether the blood or tissue antibiotic concentrations achieved exerted any harmful effects could not be evaluated in this group of patients.

TABLE V
INCIDENCE OF INFECTION IN PATIENTS WITH POST-TRAUMATIC RENAL INSUFFICIENCY

Data	No. Patients with Adequate Records	No. Patients Affected	Per cent Patients Affected
1. Site of infection			
(a) *Wound*, including peritonitis or empyema in missile tract	45	38	84
(b) *Pulmonary*, including purulent tracheal secretions; lung and pleura not in missile tract	39	30	77
2. Fever	39	37	95
3. Leukocytosis*	38		
(a) 10–20 thousand/mm.^{3}	15		
(b) 20–30 thousand/mm.^{3}	16		
(c) Over 30 thousand/mm.^{3}	7		

* Highest recorded value during course.

Peritonitis and/or empyema (localized or generalized) were found in sixteen or roughly

one-third of patients with adequate records. An additional ten patients had extensive infection of buttock or extremity wounds necessitating either reamputation or repeated débridement. Evidence of massive infection was the prominent finding at autopsy and thought to be the main cause of death in the majority of fatal cases after the artificial kidney became available.[47]

Impaired Wound Healing. Granulation tissue appeared in some open wounds between the fifth and tenth post-wound days but never in areas of infection and necrosis. Failure to slough necrotic tissue and establish a clean, granulating surface by the tenth post-wound day was taken to indicate impairment in the reparative process. Dehiscence of incisions and of vascular and even intestinal anastomoses provided another index. Dehiscences were thought to be rare in the general casualty population.[48]

In this group of patients absence of granulation and of healing of open wounds was noted beyond ten days in sixteen of twenty-four records with specific data. Dehiscence of one or another type occurred in nine instances or 16 per cent of fifty-five adequate records. In the absence of histologic studies the true incidence of delayed capillary and fibroblastic proliferation in the healing wound-sites cannot be stated, nor can the relation of these to infection, anemia, azotemia, electrolyte imbalance, edema and nutrition be established.

Bleeding Tendency and Anemia. Bleeding from the gastrointestinal tract, ecchymoses in skin, mucous and serous membranes, or epistaxis *unrelated* to trauma or unhealed surgical lesions was recorded in fifteen or 27 per cent of fifty-five patients. In two patients with serious bleeding, bleeding time, clotting time and platelet counts were normal; in two additional patients the prothrombin time was prolonged in one, normal in the other. The use of heparin during hemodialysis accelerated bleeding in only two instances. Bleeding occurred on days prior to hemodialysis and in patients not subjected to the procedure.

Low and falling hematocrits irrespective of bleeding occurred in all patients surviving for seven days or longer. In four patients hematocrits failed to rise significantly after whole blood transfusions even in the absence of, or with minimal amounts of blood loss. Frequent blood transfusions in an attempt to support blood pressure, wound healing and nutrition rendered pertinent studies impractical.

Incidence of Hypertension. Blood pressures of 140/90 mm. Hg or above were recorded in 85 per cent of forty-two patients with adequate records during the course of acute renal failure. In 70 per cent hypertensive blood pressure levels were recorded within the first four post-wound days. Most of the remaining patients who did not develop hypertension harbored severe wound infections, empyema or peritonitis. The average maximum blood pressure on the sixth post-wound day was 160/99, although readings of 180–200/100–110 were not infrequent. The clinical course was not apparently affected by the occurrence or degree of hypertension. These findings confirm observations in World War II[1,4] in which hypertension was uniformly noted in patients with acute renal failure. Elevated levels of blood pressure were also recorded in two-thirds of the patients studied by Swan and Merrill.[8]

Case 2 illustrates several of the foregoing features. Daily urine output, NPN, potassium and hematocrit values are presented in Figure 5.

A twenty-seven year old infantryman sustained traumatic amputation of his right leg at the knee with multiple penetrating wounds of both buttocks and right arm in a land mine explosion. Evacuation required five hours during which 100 ml. albumin were given. Blood pressure was unobtainable by auscultation on admission to the forward surgical hospital. At surgery, severed vessels were ligated, a traumatic rectovesical fistula was discovered and repaired, and a diverting colostomy established. Hypotension persisted for sixteen hours and 3.6 L. of whole blood were used. Oliguria persisted on the the third post-wound day and evacuation to the Renal Insufficiency Center was accomplished on the fourth.

Diuresis occurred on the twenty-third post-wound day, the most prolonged oliguria of any surviving patient. Although potassium intoxication occurred only prior to dialysis I, it is doubtful whether this patient could have survived the recurrent clinical uremia without repeated hemodialyses. Response of appetite, mental awareness and ability to cough was dramatic after dialyses I and II, less so after dialysis III. Infection was evident: a persistent cough productive of purulent sputum and a deeply lying abscess in the right popliteal fossa were noted on the fourth post-wound day. Both infection and impaired wound healing were apparent on the twentieth post-wound day when the left

leg wound was found to have necrotic skin flaps; some granulation tissue was noted in uninfected areas. On the twenty-fourth day urine appeared in the buttock wound indicating probable dehiscence of the rectovesical repair site. Wounds seemed improved on the twenty-eighth day and were granulating well by the thirty-third day. Epistaxis on the tenth post-wound day and melena between the twentieth and twenty-fourth days suggested a bleeding tendency since the patient sustained no facial or gastrointestinal wounds proximal to the colos tomy. The hematocrit remained low in spite of 8 L. of transfused whole blood between the ninth and thirty-first post-wound days. All transfusions were well tolerated. A weight loss of 17 kg. or 32 per cent of admission body weight occurred in thirty-four days, despite oral food intakes after dialyses and parenteral allowances exceeding 400 calories daily. Generalized peripheral edema is recorded on the nineteenth day; preceding average positive measured fluid balance did not exceed 500 ml. per day.

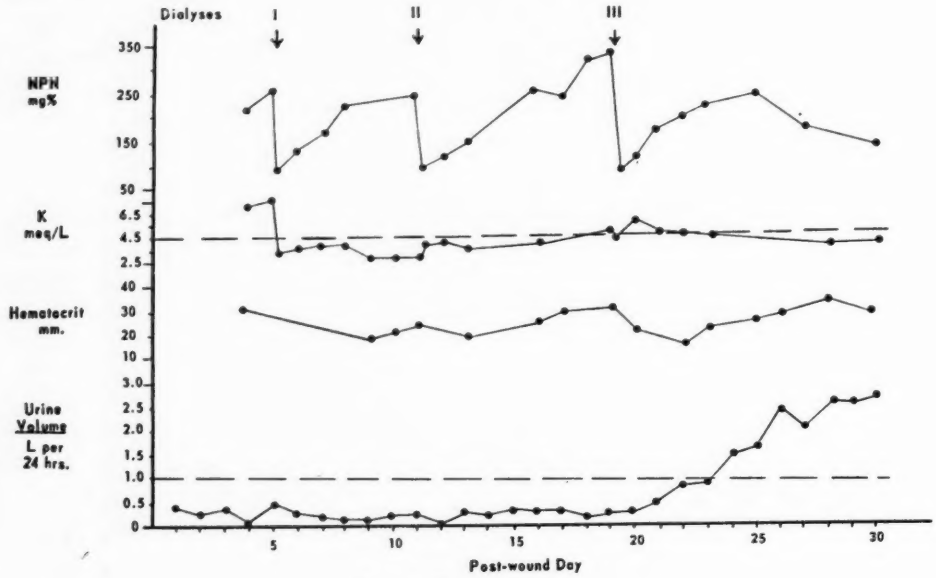

FIG. 5. Data in Case 2.

SUMMARY

Post-traumatic renal insufficiency is important as a cause of illness and death in initially surviving combat casualties and may be seen in civilian medical practice after accidents or extensive surgery. Hypotension appears to be a primary etiologic factor although delay in therapy, inadequate blood replacement, increase in plasma hemoglobin and other pigments, and the severity of the wound may contribute to the extent of renal damage and to the hypotension itself. Impairment of renal function following trauma may be reflected in different patients by sensitive clearance tests only, by azotemia and decreased urinary concentrating ability, by transient oliguria or by marked oliguria of varying duration. This suggests a wide variability in the extent of functional and parenchymal renal injury. With few exceptions, only the oliguric patients develop sufficient electrolyte abnormality or clinical uremia to require special care. In the latter instances rapidly progressive potassium intoxication necessitates prompt evacuation to a treatment center and, in the patients reported here, was the major cause of death prior to the use of hemodialysis. In addition to potassium intoxication, evidence that accelerated tissue catabolism characterizes post-traumatic renal insufficiency is found in (1) rapidly developing clinical uremia with corresponding rates of NPN accumulation, (2) early signs and marked degree of weight loss and emaciation, and (3) edema formation on less than conventional fluid intake allowances. The contrast with acute renal failure of non-traumatic origin has been repeatedly emphasized. Frequently occurring extensive and progressive infection, impaired wound healing and a marked bleeding tendency in some patients complicate the clinical course and intensify the therapeutic challenge.

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REFERENCES

1. Board for the Study of the Severely Wounded, Surgery in World War II: The Physiologic Effects of Wounds, Washington, D. C., 1952, Office of the Surgeon General, Department of the Army.
2. Mallory, T. B. Hemoglobinuric nephrosis in traumatic shock. *Am. J. Clin. Path.*, 17: 427, 1947.
3. Simeone, F. A., Schreiner, G. E., Artz, C. P. and Nelson, R. M. Unpublished data.
4. Lucké, B. Lower nephron nephrosis. The renal lesions of the crush syndrome, of burns, transfusion, and other conditions affecting the lower segments of the nephrons. *Mil. Surgeon*, 99: 371, 1946.
5. Dunn, J. S., Gillespie, M. and Niven, J. S. F. Renal lesions in two cases of crush syndrome. *Lancet*, 2: 549, 1941.
6. Ayer, G. D. and Gauld, A. G. Uremia following blood transfusion. Nature and significance of renal changes. *Arch. Path.*, 33: 513, 1942.
7. Oliver, J., MacDowell, M. and Tracy, A. The pathogenesis of acute renal failure associated with traumatic and toxic injury. Renal ischemia, nephrotoxic damage and the ischemuric episode. *J. Clin. Investigation*, 30: 1305, 1951.
8. Swan, R. C. and Merrill, J. P. The clinical course of acute renal failure. *Medicine*, 32: 215, 1953.
9. Muirhead, E. E. and Stirman, J. A. Acute progressive, unrelenting renal failure, a manifestation of severe shock associated with upper and lower nephron nephrosis. *Surgery*, 32: 43, 1952.
10. Gamble, J. L. Physiologic information gained from studies on the life-raft ration. *Harvey Lect.*, 42: 247, 1946–47.
11. Simmons, T. S. and Gentzkow, C. J. Laboratory Methods of the United States Army, p. 201. Philadelphia, 1944. Lea and Febiger.
12. Hawk, O. and Summerson, T. Practical Physiological Chemistry, 12th ed., p. 649. Philadelphia, 1951. The Blakiston Co.
13. Schales, O. and Schales, S. S. A simple and accurate method for determination of chloride in biological fluids. *J. Biol. Chem.*, 140: 879, 1941.
14. Medical Statistics Division, Office of the Surgeon General, Department of the Army, Personal communication.
15. Howard, J. M. Unpublished data.
16. Ladd, M. Personal communication.
17. Lauson, H. D., Bradley, S. E. and Cournand, A. The renal circulation in shock. *J. Clin. Investigation*, 23: 381, 1944.
18. Cournand, A., Riley, R. L., Bradley, S. E., Breed, E. S., Noble, R. P., Lauson, H. D., Gregersen, M. I. and Richards, D. W. Studies of the circulation in clinical shock. *Surgery*, 13: 964, 1943.
19. Barnett, C. H., Shapiro, S. L., Simeone, F. A., Beecher, H. L., Mallory, T. B. and Sullivan, E. R. Renal function studies in the wounded. *Surgery*, 22: 856, 1947.
20. Sanderson, P. H. Renal failure following abdominal catastrophe and alkalosis. *Clin. Sc.*, 6: 207, 1948.
21. Van Slyke, D. D. Effects of hemorrhage on the kidney. *Ann. New York Acad. Sc.*, 49: 593, 1948.
22. Yuile, C. L. Hemoglobinuria. *Physiol. Rev.*, 22: 19, 1942.
23. Cannan, R. K. and Redish, J. The large-scale production of human hemoglobin, with preliminary observations on the effect of its injection in man. Blood Substitutes and Blood Transfusion, Springfield, Ill., 1942. C. C Thomas.
24. Amberson, W. R., Jennings, J. J. and Rhode, C. M. Clinical experience with hemoglobin-saline solutions. *J. Applied Physiol.*, 1: 469, 1949.
25. Smith, H. W. The Kidney. New York, 1951. Oxford University Press.
26. Brandt, J. L., Frank, N. R. and Lichtman, H. C. The effects of hemoglobin solutions on renal functions in man. *Blood*, 6: 1152, 1951.
27. Ross, J. F. Hemoglobinuria and hemoglobinurias. *New England J. Med.*, 233: 691, 732, 766, 1945.
28. Flink, E. B. Blood transfusion studies. III. The relationship of hemoglobinemia and of the pH of urine to renal damage produced by injection of hemoglobin solution into dogs. *J. Lab. & Clin. Med.*, 32: 223, 1947.
29. Maluf, N. S. R. Factors inducing renal shutdown from lysed erythrocytes. An experimental study. *Ann. Surg.*, 130: 49, 1949.
30. Phillips, R. A., Dole, V. P., Hamilton, P. B., Emerson, K. J., Archibald, R. M. and Van Slyke, D. D. Effects of acute hemorrhagic and traumatic shock on renal function in dogs. *Am. J. Physiol.*, 145: 314, 1946.
31. Phillips, R. A. and Hamilton, P. B. Effect of 20, 60 and 120 minutes of renal ischemia on glomerular and tubular function. *Am. J. Physiol.*, 152: 523, 1948.
32. 406th Medical General Laboratory, Annual Historical Report, 1952, Tokyo, Japan.
33. Crosby, W. Personal communication.
34. Holmes, R. H. Wound ballistics and body armor. *J. A. M. A.*, 150: 73, 1952.

35. Keith, N. M. and Burchell, H. B. Clinical intoxication with potassium: its occurrence in severe renal insufficiency. *Am. J. M. Sc.*, 217: 1, 1949.
36. Marchand, J. F. and Finch, C. A. Fatal spontaneous potassium intoxication in patients with uremia. *Arch. Int. Med.*, 73: 384, 1944.
37. Merrill, J. P., Levine, H. D., Somerville, W. and Smith, S. Clinical recognition and treatment of acute potassium intoxication. *Ann. Int. Med.*, 33: 797, 1950.
38. Levine, H. D. and Merrill, J. P. Advanced disturbances of the cardiac mechanism in potassium intoxication in man. *Circulation*, 3: 889, 1951.
39. Currens, J. H. and Crawford, J. D. Electrocardiogram and disturbance of potassium metabolism. *New England J. Med.*, 243: 843, 1950.
40. Moore, N. S. and Stewart, H. J. Disappearance of intraventricular heart block occurring in uremia following intravenous injection of hypertonic glucose solution. *Am. Heart J.*, 5: 469, 1930.
41. Teschan, P. E. and McDowell, M. E. Artificial kidney. *Armed Forces M. J.*, 3: 391, 1952.
42. Strauss, M. B. Acute renal insufficiency due to lower nephron nephrosis. *New England J. Med.*, 239: 693, 1948.
43. Moore, F. D. The Metabolic Response to Surgery. Springfield, Ill., 1952. C. C Thomas.
44. Frawley, J. P. Personal communication.
45. Rush, B. F., Jr., Teschan, P. E. and Post, R. S. The metabolic response in patients with acute renal failure associated with massive tissue destruction and infection. (In preparation.)
46. Leaf, A. and Camara, A. A. Renal tubular secretion of potassium in man. *J. Clin. Investigation*, 28: 1526 1949.
47. Smith, L. H., Jr., Post, R. S., Teschan, P. E., Abernathy, R. S., Davis, J. H., Gray, D. M., Howard, J. M., Johnson, K. E., Klopp, E., Mundy, R. L., O'Meara, M. P. and Rush, B. F., Jr. Post-traumatic renal insufficiency in military casualties. II. Management and prognosis. *Am. J. Med.*, 18: 187, 1955.
48. Ziperman, H. Formerly Surgical Consultant to the Surgeon, 8th Army. Personal communication.

Post-traumatic Renal Insufficiency in Military Casualties*

II. Management, Use of an Artificial Kidney, Prognosis

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DURING the past few years there has been widespread interest in the treatment of acute renal failure of diverse origins by medical management alone,[1,2] or by the added use of some means for reversing the chemical changes of uremia, such as the artificial kidney,[3] peritoneal lavage[4] and gastric or intestinal lavage.[5] The majority of uncomplicated cases of acute renal failure can be successfully maintained until the onset of diuresis by carefully avoiding overhydration and providing sufficient calories to minimize protein catabolism. The artificial kidney has found its chief use in civilian medicine as an adjunct to medical management, occasionally life-saving in cases of spontaneous potassium intoxication or severe uremic intoxication.[5]

Patients with renal insufficiency following trauma present special problems in management because clinical uremia, high levels of azotemia and kalemia, and myocardial potassium intoxication develop rapidly.[6] Conventional methods of therapy are frequently insufficient to limit the rapid progression of uremia either in civilian practice[7] or in battle casualties. A mortality rate of approximately 80 to 90 per cent was found in casualties with post-traumatic renal insufficiency in World War II[8] and in the Korean War. Because of this excessive mortality rate a Renal Insufficiency Center was established in Korea in an attempt to improve the therapeutic results. An evaluation of the Brigham-Kolff artificial kidney in post-traumatic renal insufficiency was carried out at this center.

ORGANIZATION OF RENAL INSUFFICIENCY CENTER

Through the cooperation of the Eighth Army, the Renal Insufficiency Center was established at a large evacuation hospital in central Korea about 70 miles from the front. The importance of such a location is the accessibility within helicopter range of the forward hospitals, where most of the cases of post-traumatic renal insufficiency occur. The average period of time between wounding and arrival at the Center was 3.2 days in the fifty-one patients admitted during 1952.

Patients who survived remained at the Renal Insufficiency Center until diuresis and sufficient recovery made it possible for them to re-enter the regular chain of evacuation safely. A laboratory capable of carrying out all of the usual clinical chemistries was established. The chemical methods used have been listed in the accompanying paper.[6] A Brigham-Kolff type of artificial kidney was utilized, consisting of a partially submerged rotating drum with a continuous helically wound cellophane tube of approximately 20,000 cm.^{2} surface area. The technic of operating this type of artificial kidney has been described in detail.[9] The usual dialysis was carried out for six hours at a blood flow rate of 250 to 350 cc./minute. Occasionally, when hyperkalemia was the only indication, dialysis was limited to three or four hours.

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MEDICAL TREATMENT

The principles of the medical management of acute renal failure have been well described elsewhere.[1,2] Within the limitations imposed by the severity of the wounds in this group of patients, these principles were followed in the manner outlined:

Oliguric Phase. 1. *Fluid restriction:* Fluid intake was initially restricted to a maximum of 600 to 800 cc. per twenty-four hours (a rough estimate of insensible loss) plus the estimated loss of urine, drainage from wounds and gastric or intestinal suction. The presence of fever and sweating, and an unknown amount of endogenous water production from catabolism, limited the accuracy of the fluid balance. Careful daily weights taken on a stretcher-type bedside balance were of great value as a check on fluid requirements. An attempt was made to maintain a steady decrease in body weight throughout the oliguric period. A marked loss of body mass occurs during the catabolic phase of acute renal failure, which is often masked by fluid retention until after diuresis.[10] A program to produce a gradual decline in weight rather than maintenance of the initial weight during the oliguric phase of acute renal insufficiency prevents "relative overhydration." During their care at the Renal Insufficiency Center almost all of the patients required repeated transfusions or underwent such surgical procedures as amputation or débridement. This placed restrictions on the over-all reliability of daily weights as an index of fluid balance.

2. *Caloric intake:* The end-products of carbohydrate and fat catabolism are carbon dioxide and water, both of which can be eliminated by way of the lungs. Protein catabolism imposes the main excretory burden of the kidneys. With the loss of protein there is also loss of other intracellular components, especially potassium. Although the uremic syndrome cannot at present be related to a specific chemical change, the severity of uremic symptoms appeared to vary approximately with plasma NPN concentrations during oliguria. Suppression of protein catabolism by supplying carbohydrate and fat to the metabolic pool should therefore be attempted. Gamble demonstrated that 100 gm. of glucose would prevent ketosis and reduce the negative N balance by 50 per cent in normal fasting men.[11] An increase of carbohydrate intake to 200 gm. did not produce a further significant reduction in protein catabolism. An attempt was therefore made to supply at least 100 gm. glucose per day, giving the daily basal fluid requirement as 15 per cent glucose in a peripheral vein. Repeated observations of profound tissue wasting led to increased use of 50 per cent dextrose infused into cannulated major veins. Seventy-one per cent of the patients treated at the Renal Insufficiency Center had abdominal wounds which restricted attempts to give high caloric regimens by mouth. Oral feeding was instituted as soon as possible in all cases.

3. *Treatment of acidosis, hyponatremia and hypochloremia:* Hyponatremia and hypochloremia were already in evidence in the majority of the fifty-one patients at the time of admission to the Renal Insufficiency Center, an average of 3.2 days after wounding. The average admission plasma values were sodium 133 mEq./L. (range of 113–164), chloride 87 mEq./L. (62–108) and carbon dioxide 24.2 mEq./L. (14.8–43.4). The subsequent values of sodium, chloride and carbon dioxide varied markedly depending on the treatment. Despite rigid fluid restriction, there was a general tendency toward further decreases in plasma sodium and chloride during the oliguric period, suggesting intracellular shifts or progressive hydration from endogenous water production. The plasma values were usually returned to normal during dialysis with the artificial kidney, as will be discussed subsequently. Because of the danger of producing pulmonary edema, hypertonic saline solution was given only as necessary to reduce the toxicity of any concurrent hyperkalemia and to raise plasma sodium levels which had fallen below 115 to 120 mEq./L. There was usually a gradually increasing metabolic acidosis during the oliguric period, reflecting the retention of fixed acids. Here also treatment with sodium lactate or sodium bicarbonate was usually given only if acidosis was severe (CO_2 combining power below 12 to 15 mEq./L.). Occasionally, metabolic alkalosis secondary to gastric suction was found on admission and in one patient required ammonium chloride therapy. Treatment with the artificial kidney invariably returned the acid-base balance toward normal although this reversal was seldom complete.

4. *Treatment of anemia:* Progressive anemia is a frequent finding in acute renal failure of any origin. Although the mechanism is not entirely understood, it seems probable that both decreased blood formation and increased blood

destruction occur during uremia.[10] The picture is complicated in the present series of patients by the large amounts (average of 6 L.) of relatively old (two weeks) type O blood which they had received during resuscitation. A study of the limited survival time of this blood is presented in another paper from the Surgical Research Team.[12] In addition, recurrent bleeding from various sites in these patients required large amounts of blood for replacement purposes.[6] Despite the fact that their admission hematocrits averaged 40 per cent, the fifty-one patients in this series required an average of 4,950 cc. (range 0–13,000 cc.) of fresh, type-specific blood during an average period at the Renal Insufficiency Center of 12.9 days (range three hours to thirty-three days). In the first patients transfusions were rarely given electively for a moderate reduction in hematocrit because of the danger of pulmonary edema. When wound healing was a problem, however, packed red cell transfusions were given with increasing frequency to maintain the hematocrit in excess of 35 per cent. These were well tolerated. It was noted on several occasions that patients could tolerate large amounts of blood during and immediately following hemodialysis despite having previously developed pulmonary edema during the infusion of much smaller volumes of blood.

5. *Treatment of hyperkalemia:* The frequency of hyperkalemia and the rapidity with which it developed in this group of patients were noted in the accompanying paper.[6] Plasma potassium values were measured daily or oftener if they seemed to be rising rapidly. Electrocardiographic tracings were usually obtained at the time of potassium analysis in all patients with significant elevations of plasma potassium, and were relied upon to estimate the seriousness of the medical emergency.

The physiologic antagonism between extracellular potassium and sodium or ionized calcium was made use of in the emergency treatment of acute potassium intoxication. Hypertonic saline solution (200–400 cc. of a 3–5% solution) was given if the plasma sodium was below normal. The use of calcium in the treatment of hyperkalemia received a much more thorough evaluation at the Renal Insufficiency Center during the six months following the period covered in the present report and will be presented in a separate communication.[13] In the treatment of acute hyperkalemia large amounts of 50 per cent glucose and insulin (1 unit per 2 to 3 gm. glucose) also were given intravenously to reduce extracellular potassium by inducing its intracellular deposition with glycogen.[14] These measures were at best only temporarily effective and were usually followed within a few hours by emergency dialysis by use of the artificial kidney.

An ammonium carboxylic cation exchange resin* was used both in the treatment of acute potassium intoxication and in an attempt to maintain normal potassium levels after hemodialysis. A dose of 25 gm. of resin as a 10 per cent suspension in water was usually given once or twice daily by retention enema or in divided doses over several hours orally. The high incidence of abdominal wounds (71 per cent) seriously limited the usefulness of the resins in severely wounded patients. Use of the resin in the treatment of acute potassium intoxication was disappointing since the plasma potassium levels usually remained elevated or even rose despite administration early in the clinical course. In the absence of severe abdominal wounds, the resin could be regularly employed and seemed of considerable value in preventing a secondary rise in plasma potassium after normal values had been established by hemodialysis.[15]

The use of the artificial kidney in the treatment of hyperkalemia will be discussed in the following section.

Diuretic Phase. The beginning of diuresis (600 cc. of urine per twenty-four hours) by no means marks the end of the therapeutic problems. In the present series one-third of the deaths (nine of twenty-seven) occurred after the onset of diuresis. Several days of diuresis were usually required to bring about significant chemical and clinical improvement. Because of this delayed response seven of the seventy-two dialyses with the artificial kidney were carried out after the onset of diuresis. Fluids were given in proportion to the degree of diuresis but no effort was made to maintain a constant weight. Most patients lost weight at the time of diuresis, indicating previous overhydration despite rigid fluid restriction. Urinary sodium was measured and was partially but not quantitatively replaced. As emphasized by Swan and Merrill,[10] quantitative replacement of sodium loss during the early diuretic phase is not necessary and may

* SKF#648. This was kindly supplied to us by the Smith, Kline and French Laboratories.

prolong diuresis. No patient developed clinical or chemical sodium depletion during this phase. The hypernatremia-hyperchloremia syndrome described by Luetscher and Blackman[18] was not observed in this series. Most of the deaths during the diuretic phase were attributable to complications of wounding, as will be further discussed.

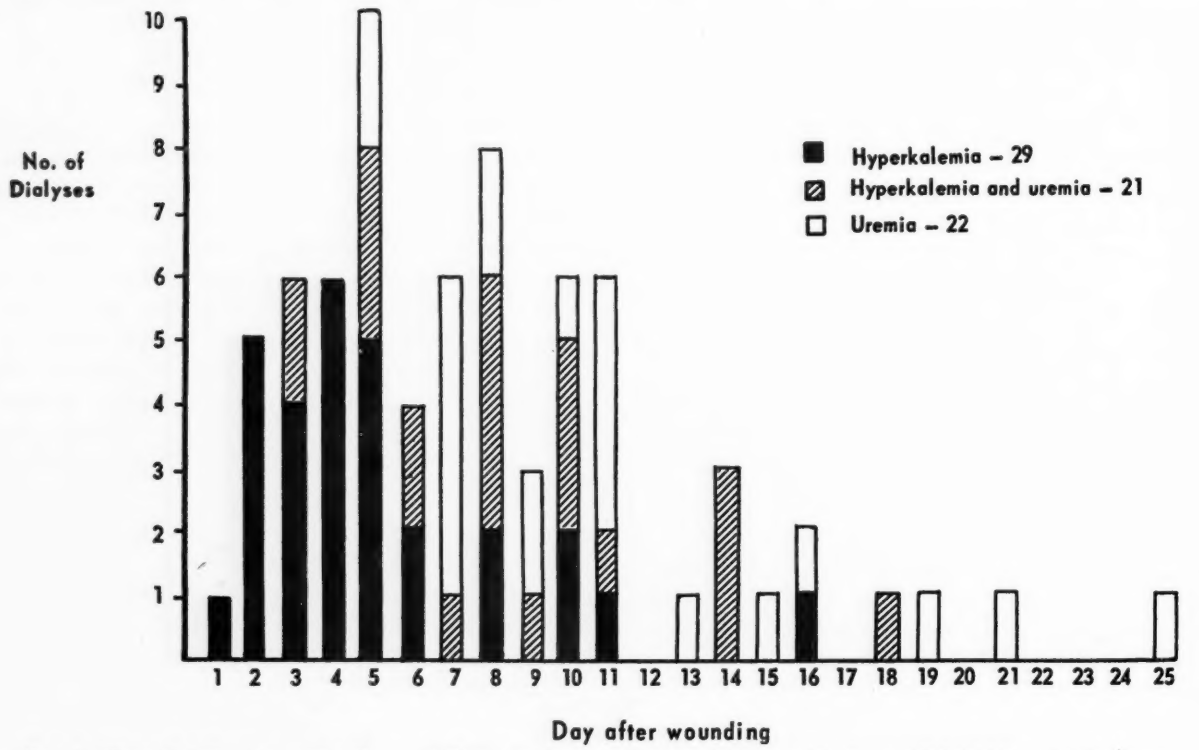

FIG. 1. Time distribution and primary indications for seventy-two dialyses with the artificial kidney in the treatment of thirty-one patients.

USE OF THE ARTIFICIAL KIDNEY

Number of Dialyses and Indications. Dialysis with the artificial kidney was carried out seventy-two times in thirty-one of the fifty-one patients (about 60 per cent) treated at the Renal Insufficiency Center. The artificial kidney was not used in twenty patients for a variety of reasons such as relative mildness of uremia or early death from complications attending wounds. The number of treatments received by the individual patients varied from one to six: one dialysis, nine patients; two dialyses, ten patients; three dialyses, nine patients; four dialyses, one patient; six dialyses, two patients.

Figure 1 presents the time distribution of the dialyses following wounding. Also shown are the primary indications for the individual dialyses: hyperkalemia, twenty-nine dialyses; marked uremia without significant hyperkalemia, twenty-two dialyses; marked uremia accompanied by hyperkalemia, twenty-one dialyses. This classification of indications is somewhat arbitrary but demonstrates the trend toward early development of potassium intoxication. One patient required dialysis for hyperkalemia on the first day after being wounded.

The indications for use of the artificial kidney at the Renal Insufficiency Center were not rigidly defined but depended on clinical judgment in each case. In general, dialysis was carried out if electrocardiographic evidence of myocardial intoxication was marked. Dialysis was almost always carried out if the plasma potassium value was greater than 7.5 mEq./L., since definite electrocardiographic changes of myocardial potassium intoxication were then invariably present. The average plasma potassium value at the time of dialysis both in the group termed "hyperkalemia" and in that designated "uremia plus hyperkalemia" was 7.1 mEq./L. While plasma potassium values of less than 9.0 mEq./L. are seldom fatal, the decision to carry out dialysis in the plasma potassium range of 6.5 to 7.5 mEq./L., even with electrocardiographic changes limited to the T

wave alone, was based on the observed rapidity with which plasma potassium rose in this series of patients and the usual concomitant presence of hyponatremia and hypocalcemia. Early in this experience, before the establishment of the Renal Insufficiency Center, plasma potassium rose from 8.0 mEq./L. to a fatal level of 11.2 mEq./L. within a day in one patient despite the use of cation exchange resins. Another patient died in cardiac arrest after his plasma potassium rose from 6.1 mEq./L. to 9.1 mEq./L. within a single day. It was thought advisable, therefore, to carry out dialysis electively at relatively low levels of hyperkalemia to diminish the risk of acute elevations in extracellular potassium concentration and consequent myocardial intoxication.

Twenty-two of the dialyses were carried out for uremia without significant hyperkalemia and twenty-one dialyses for uremia accompanied by hyperkalemia. At the time of treatment the average serum NPN values in these two groups were 275 mg. per cent and 308 mg. per cent, respectively. The decision to use the artificial kidney was not based on the level of azotemia, which in one patient was allowed to rise to 504 mg. per cent, but on the severity of the clinical signs and symptoms of uremia, especially clouding of consciousness with inability to clear tracheal secretions by coughing, marked nausea and vomiting with restriction of caloric intake, signs of neuromuscular irritability and dyspnea. On several occasions dialyses were carried out with milder degrees of uremia or hyperkalemia to prepare an oliguric patient for a major surgical procedure such as amputation or extensive débridement.

Results of Treatment. The effects of an uncomplicated six-hour dialysis on blood electrolytes in the treatment of uremia can be predicted with reasonable accuracy. The plasma sodium, potassium and chloride concentrations return to normal levels if abnormal initially. The CO_2 combining power, as an index of acidosis, returns toward but does not usually attain a normal value. The serum NPN level is usually reduced to 75 mg. per cent to 125 mg. per cent, depending on its initial value and the flow rate of blood maintained through the artificial kidney. The average changes in blood electrolytes for the seventy-two dialyses are shown in Table 1.

TABLE 1

AVERAGE RESPONSES OF SERUM ELECTROLYTES TO DIALYSIS WITH THE ARTIFICIAL KIDNEY*

Dialyses	NPN (mg. %)	K (mEq./L.)	Na (mEq./L.)	Cl (mEq./L.)	CO_2 (mEq./L.)
1. Total dialyses—72					
Before	246	6.5	135	92	17.2
After	108	4.3	138	105	21 4
2. "Hyperkalemia dialyses"—29					
Before	191	7.1	132	...	....
After	93	4.3	139	...	....
3. "Hyperkalemia plus uremia dialyses"—21					
Before	308	7.1	138	...	....
After	123	4.4	141	...	....
4. "Uremia dialyses"—22					
Before	275	5.0	143	...	....
After	120	4.1	141	...	....

* Average duration of the seventy-two dialyses, 5.3 hours.

The clinical results of treatment with the artificial kidney are not as easy to appraise. Occasionally there was clinical improvement during the course of the dialysis as shown by an objective clearing of consciousness or decrease in dyspnea, or a spontaneous statement from the patient that he felt much improved. Maximal clinical improvement was usually noted in twelve to twenty-four hours after treatment and was particularly evident in loss of nausea and vomiting, return of appetite, clearing of consciousness and decrease in dyspnea. The subjective improvement was sometimes of such degree that several patients requested another

dialysis after the return of uremic symptoms during continued oliguria. Noted previously was the fact that patients were often able to receive transfusions of whole blood during and soon after dialysis without respiratory distress, although smaller amounts of blood given prior to treatment with the artificial kidney led to dyspnea and early pulmonary edema. Not all of the patients treated with the artificial kidney demonstrated noticeable clinical improvement despite the usual chemical changes. This clinical refractoriness was found only in patients with unusually severe wounds or complications of wounds.

The results of treatment with the artificial kidney in terms of survival value will be discussed under prognosis.

Complications of Dialysis. The use of the artificial kidney is not without risk, especially in such desperately ill patients. Operational difficulties in the dialyses, such as the development of a leak in the dialyzing membrane or clotting of blood in the return reservoir, were rare and did not seriously affect the completion of dialysis. The complications observed in the patients were:

1. *Hypertension:* Progressive hypertension has been previously described as occurring in ten to fifteen per cent of patients undergoing dialysis.[3] The development of hypertension cannot be predicted in the individual case. Its cause remains obscure. Excluding dialyses complicated by excessive bleeding and transfusions, in fourteen of forty-nine dialyses (29 per cent) without initial hypertension (B.P. less than 150/90) there was a significant rise in blood pressure from a mean initial value of 135/74 to a mean maximal value of 215/109. In one patient the blood pressure rose from an initial level of 180/100 to 270/130 mm. Hg. The elevation of blood pressure usually occurred progressively, beginning after one or two hours of treatment with the artificial kidney. Occasionally apresoline® was used to lower or prevent further elevation of blood pressure. No clinical complications could be attributed to this hypertensive effect of dialysis in the present series of patients. In several patients with initial hypotension despite repeated transfusions, blood pressures rose and became stabilized during dialysis.

2. *Periods of hypotension:* Blood pressures less than 100/60 were recorded in twelve of seventy-two dialyses, excluding those patients who were hypotensive before entering the operating room. The fall in blood pressure usually occurred during cannulation of the artery and vein under local procaine anesthesia or during the early period of dialysis when flow through the artificial kidney was being established. Response to transfusion was rapid in most cases, with a return to normal blood pressure. Hypotension occurring during dialysis was usually related to bleeding from the patients' wounds and responded to transfusion.

3. *Bleeding:* Many of the patients who received treatment with the artificial kidney had been severely wounded within seventy-two hours prior to dialysis and extensive, reparative surgical procedures had been done. Furthermore, during their treatment at the Renal Insufficiency Center approximately one of every four patients had bleeding episodes unrelated to previous trauma, such as cutaneous ecchymoses, epistaxes and bleeding from the gastrointestinal tract. During dialysis, intravenous heparin, 50 to 120 mg., was given to prevent the blood from clotting during its circulation through the artificial kidney and return reservoir, a period of approximately two minutes. The occurrence of hypertension during dialysis has already been noted. With this combination of predisposing factors it was anticipated that hemorrhage would be the major complication of dialysis in such a series of recently wounded soldiers. It is therefore surprising that only two patients exhibited bleeding of sufficient degree to cause hypotension and necessitate stopping dialysis. Brisk bleeding from a wound involving the rectum and urethra in one patient was controlled by packing and the use of protamine sulfate intravenously. The second patient had extensive wounds of the liver, right kidney, diaphragm and jejunum. Three days before dialysis, on the thirteenth day after wounding, an emergency laparotomy had to be performed to control bleeding from the hepatic wounds. During the night prior to dialysis five pints of whole blood were required to maintain blood pressure because of bleeding from the abdominal wound and liver. Because of severe uremia and potassium intoxication, dialysis was carried out on the sixteenth day after wounding. There was exacerbation of bleeding during the procedure, requiring repeated transfusion. The patient died in shock sixteen hours after dialysis. Some oozing of blood was frequently seen from open débrided wounds, amputation stumps and the cutdown sites for cannulation of the artery and the vein. This was easily controlled, however, without interfering

with completion of dialysis. Sites from which bleeding could be anticipated were usually packed before beginning the procedure.

4. *Fever:* In 55 per cent of the dialyses the oral or axillary temperature rose above 100°F. from a previously normal value, and rarely (five times) the temperature reached 103° to 104°F. During six dialyses shaking chills were observed, with no evidence of hemolysis. The fever was probably related to pyrogenic contamination of the water supply obtained under field conditions. This represents a much higher rate of febrile reactions than that observed under more ideal operating conditions.

SURGICAL MANAGEMENT

The limiting factor in survival for most patients was the severity of the initial wound and its subsequent complications rather than renal damage *per se*. Radical débridement of wounds, early amputation of areas of gangrene and continued careful search for localized infection subject to drainage were of the utmost importance in patients with reduced renal function. On a number of occasions the rapid progression of uremia was blunted by the discovery and drainage of an abscess or amputation of a mangled extremity. Also of great practical importance was the frequency of pulmonary complications. In these patients with malnutrition, weakness, clouding of consciousness and nausea over periods of one to three weeks, atelectasis and bronchopneumonia were constant hazards. Tracheal suction, the use of a Stryker frame and even tracheotomy were some times necessary to maintain adequate pulmonary function.

PROGNOSIS

Control Mortality—(prior to availability of the artificial kidney). In World War II there was a mortality rate of 91 per cent in casualties who developed oliguria of less than 100 cc. per day.[8] On arrival in Korea a survey of the forward hospital units was carried out by the Surgical Research Team to determine the incidence and mortality rate of post-traumatic renal insufficiency among the military casualties. It was found during the preceding three months approximately fifty oliguric patients were treated at these hospitals, with a mortality rate of 80 to 90 per cent. During the same period of time Moots reported the death of eight of nine patients with post-traumatic renal insufficiency at a single forward hospital.[16] Before the artificial kidney was available and the Renal Insufficiency Center was established in Korea ten casualties with acute renal failure were treated under the supervision of the Surgical Research Team using the medical regimen already described. Eight of these ten patients died, with an average survival time of 6.8 days after wounding. Although these "control" groups are not as large or as strictly comparable as might be wished, it seems likely that the mortality rate of post-traumatic renal insufficiency with oliguria in military casualties approximates eighty to ninety per cent even in patients receiving intensive medical therapy. Many of the deaths, however, are not due to uremia *per se* but to the severity of the attending wounds.

Mortality Rate at Renal Insufficiency Center. During the last eight and one-half months of 1952 fifty-one patients with post-traumatic renal insufficiency were treated at the Renal Insufficiency Center. Thirty-one of the patients (61 per cent) received one or more dialyses with the artificial kidney, with an average of 2.3 dialyses per patient. Twenty-one of these thirty-one patients (68 per cent) died, death occurring at an average time interval of 12.4 days after wounding. Of the twenty patients who were treated without use of the artificial kidney six died, a mortality rate of 30 per cent. It is to be emphasized that this group of patients in no way represents a control for those treated by dialysis. Only the least severe cases of acute renal failure, without marked uremia or dangerous hyperkalemia, were treated by medical management alone. The six patients who died in this medically treated group were found clinically and at autopsy to have either overwhelming infection or hemorrhage, rather than uremia, as the cause of death. The combined mortality rate for the fifty-one patients was 53 per cent. This is the figure of greatest significance in evaluating the over-all effectiveness of the Renal Insufficiency Center. Table II summarizes these mortality figures and includes a summary of other data available for comparison.

Cause of Death. Despite the efficacy of dialysis in returning electrolyte abnormalities toward normal and usually in improving the signs and symptoms of uremia, approximately two-thirds of treated patients died within a time interval varying from five to twenty-eight days after wounding. In almost every case death was attributable to some complication of the initial

wound, such as infection or secondary hemorrhage. Six illustrative cases are listed in Table III.

ILLUSTRATIVE CASES

The following two case histories are presented to illustrate (1) the successful use of the artificial kidney and (2) failure of dialysis to prevent a fatal outcome despite temporary improvement in serum electrolytes.

TABLE II

SUMMARY OF THE MORTALITY RATES AND SURVIVAL TIMES OF MILITARY PATIENTS WITH POST-TRAUMATIC RENAL INSUFFICIENCY IN THIS AND OTHER SERIES

Patients	Lived	Died	Mortality Rate (%)	Av. Survival Time after Wounding of Patients Who Died
1. Renal Insufficiency Center:				
Treated with artificial kidney	10	21	68	12.4 days
Treated without artificial kidney	14	6	30	10.3 days
Total group	24	27	53	12.0 days
2. "Control cases"	2	8	80	6.8 days
3. Cases of Moots[16]	1	8	89	?
4. Survey Cases of the Surgical Research Team	Approx. 50–60 cases		ca. 80–90	?
5. World War II[8]*	3	30	91	43% within 5 days 91% within 10 days

* These figures are for patients with "anuria," i.e., less than 100 cc. urine on at least one day, and in general the severest cases of post-traumatic renal insufficiency. Their over-all mortality rate for "oliguria" (65 per cent) cannot be used here because the group contained all patients with less than 600 cc. of urine for a single day. At least 35 per cent of these transiently oliguric patients did not develop serum NPN levels greater than 65 mg. per cent, and would not have been included in the other comparative series.

CASE 28. This twenty-five year old infantryman was wounded by mortar fire, receiving multiple wounds of both legs and his left arm. Compound fractures of both tibias and fibulas were present as well as numerous soft tissue wounds. Despite a 2,500 cc. transfusion of whole blood prior to and during his operation, the patient's blood pressure remained at 75–100/50–70 throughout the two and one-half-hour procedure at which the fractures were reduced and the wounds débrided. During the next few days marked oliguria was noted. Five days after injury he reached the Renal Insufficiency Center, nauseated, drowsy and complaining of numbness of his extremities and a feeling of generalized weakness. On physical examination he appeared pale, drowsy and acutely ill. Pulse was 110 and blood pressure 140/80. His hand grip was weak but reflexes were active. Both legs and his left hand were in casts. An electrocardiogram revealed elevation and peaking of the T waves and broadening of the QRS complex indicative of potassium intoxication. The plasma K was 8.6 mEq./L. Hypertonic glucose and insulin were given as an emergency measure, with reduction of the plasma K to 7.4 mEq./L. Dialysis with the artificial kidney was carried out for six hours with the following results:

	NPN mg. %	K mEq./L.	Na mEq./L.	Cl mEq./L.	CO_2 mEq./L.
Pre-dialysis	268	7.4	137	90	19.8
Post-dialysis	76	4.2	140	104	25.3

During the dialysis the patient showed considerable clinical improvement, with disappearance of his nausea and the feeling of numbness and weakness. He stated that he felt much better. The following day under general anesthesia the patient's left lower leg was amputated because of early gangrene and his other wounds débrided. He tolerated the anesthesia and surgery without difficulty. Severe oliguria continued and over the next five days the patient again became weaker and nauseated. Despite the use of 60 gm. of cationic exchange resin by retention enema each day, the plasma K rose to 7.1 mEq./L. with a return of the T

TABLE III

CAUSES OF DEATH IN SIX PATIENTS WHO DIED DESPITE TREATMENT WITH THE ARTIFICIAL KIDNEY*

Case	Initial Wound	No. of Dialyses	Day of Death	Cause of Death
4	Abdominal injury by penetrating missile with surgical removal of spleen and left kidney; repair of the stomach, gallbladder and jejunum, and colostomy for perforation of the transverse colon	3	15	Peritonitis, gangrene of a segment of jejunum; shock following extensive bleeding from the wound of exit and from the infarcted bowel
5	Concussion and contusion of abdomen in a truck accident, with rupture of spleen and right kidney, tear of duodenum and avulsion of common bile duct from it, tear of portal vein; spleen and right kidney were removed at operation and duodenum and portal vein repaired	3	16	Portal vein thrombosis with ascites and hemorrhagic colitis and ileitis; peritonitis and a small subhepatic abscess
8	Shrapnel wounds with extensive laceration and destruction of the liver, fracture of two ribs and a compound fracture of the right arm, multiple small wounds of both legs	3	9	Patient died in irreversible shock with hemorrhage into and necrosis of the right lobe of the liver and bile peritonitis
18	Shrapnel wound penetrating sacrum with laceration of rectum and retroperitoneal hematoma; multiple wounds of legs, later requiring amputation of the right leg below the knee; at the initial operation, the rectum was repaired and a colostomy performed	2	5	Patient developed irreversible shock despite vigorous transfusion with fresh cross-matched blood; it was believed that the extensive grossly infected wound involving the left buttock and sacrum and extending into the pelvic cavity contributed largely to his shock
24	Shell fragments caused laceration of the right diaphragm, liver and shattering of the right kidney; nephrectomy was done and repair of the diaphragm and liver carried out	4	25	Death seemed attributable to infection—with empyema, bronchopneumonia, atelectasis and pneumothorax; progressive diuresis never occurred during this long course, although the urine volume reached 1,200 cc. on one day
27	Penetrating wound of right lower chest with lacerations of the liver, gallbladder, duodenum and pancreas; gallbladder was removed and the other lacerations repaired	1	14	Patient had only one dialysis for hyperkalemia (8.4 mEq./L.); diuresis occurred on the 7th day and was going well when there was death from abdominal hemorrhage secondary to separation of the duodenal laceration and from a penetrating ulcer of the stomach

* An autopsy was performed in each case.

wave peaking in the electrocardiogram. Another six-hour dialysis was therefore performed on the tenth day of oliguria, with the following chemical results:

	NPN mg. %	K mEq./L.	Na mEq./L.	Cl mEq./L.	CO_2 mEq./L.
Pre-dialysis	256	7.1	135	95	14.0
Post-dialysis	106	3.7	141	102	20.0

Again there was symptomatic improvement during and immediately following the dialysis. The patient was able to take food by mouth. Four days after this dialysis the urine volume had reached 615 cc. per twenty-four hours but nausea, drowsiness and weakness recurred. Again the electrocardiogram demonstrated peaking of the T waves and slight broadening of the QRS complex. A third six-hour dialysis was therefore carried out on this fourteenth day of oliguria, with the following chemical results:

	NPN mg. %	K mEq./L.	Na mEq./L.	Cl mEq./L.	CO_2 mEq./L.
Pre-dialysis	322	7.5	131	90	14.2
Post-dialysis	191	4.7	140	102	23.8

During this dialysis urea was placed in the bath at a nitrogen concentration of 120 mg. per cent to maintain an osmotic load on the recovering kidneys during this beginning diuresis. This explains the failure of the serum NPN to drop as much as usual. The patient described "clearing of his head" and loss of nausea within a few hours after dialysis. The gradual diuresis continued, reaching 1,130 cc. on the sixteenth day; but the NPN and plasma K did not begin to fall until the nineteenth day when the urine output reached 3,000 cc./day. Convalescence thereafter was uneventful.

CASE 26. This twenty-one year old soldier was wounded by grenade fragments, with a penetrating wound of the right flank and right abdomen. At the forward hospital 2,000 cc. of blood were given to combat deep shock. Laparotomy revealed a retroperitoneal hematoma, laceration of the right kidney, a small laceration of the duodenum and three lacerations of the inferior vena cava, two above the right renal vein and one at the entrance of the left renal vein. The right kidney was removed and the duodenum was repaired. Attempts to repair the inferior vena cava were unsuccessful so clamps were left in place partially occluding the vena cava and the left renal vein and protruding from the anterior abdominal wall. Severe blood loss during the procedure necessitated infusion of 8,500 cc. of whole blood to maintain his blood pressure. Because of persistent oliguria the patient was transferred to the Renal Insufficiency Center three days after wounding. On entry the patient was alert and cooperative. Blood pressure was 140/90, and the general physical examination was normal except for the abdominal wounds. The plasma potassium was 7.2 mEq./L. but there were minimal T wave changes in the electrocardiogram. Sixty gm. of the cation exchange resin were given by retention enema, as well as hypertonic glucose with insulin. The following day there was a definite increase in the amplitude of the T waves and some widening of the QRS complex. A four-hour dialysis was performed:

	NPN mg. %	K mEq./L.	Na mEq./L.	Cl mEq./L.	CO_2 mEq./L.
Pre-dialysis	296	6.9	134	78	15.3
Post-dialysis	174	3.9	144	99	23.1

During the following four days the patient did well clinically, and the daily urine volume gradually rose to 1,000 cc. He received a total of 120 gm. of resin by enema and gastric suction was maintained in an attempt to prevent recurrence of hyperkalemia. Despite this therapy the serum K rose again and the electrocardiogram revealed signs of potassium intoxication. The patient was drowsy, nauseated and dyspneic. Another four-hour dialysis was therefore carried out on the eighth day after wounding:

	NPN mg. %	K mEq./L.	Na mEq./L.	Cl mEq./L.	CO_2 mEq./L.
Pre-dialysis	304	7.5	134	80	10.9
Post-dialysis	148	4.3	139	93	19.3

Following this dialysis the urine volume rose steadily and the patient was much improved. The plasma NPN and K rose for two more days and then gradually fell with the continuing diuresis. Thirteen days after wounding, when the plasma K was 3.7 mEq./L. and the NPN 204 mg. per cent, the clamps were removed from the inferior vena cava under general anesthesia. There was transient hypotension, responding to 500 cc. of whole blood. Two days later he complained of generalized abdominal pain and went into shock. A laparotomy was performed and revealed brisk bleeding from the inferior vena cava. Because the vein wall was friable, ligation was performed just below the renal veins. The patient died in irreversible shock several hours later, despite infusion of a total of 7,500 cc. of whole blood before, during and after the operation. Autopsy revealed a massive hemoperitoneum with the bleeding originating from a laceration at the junction of the left renal vein with the inferior vena cava.

COMMENTS

The therapeutic problems presented by military casualties with post-traumatic renal insufficiency differ only in degree from those that arise during the treatment of acute renal failure in civilian practice. This is an important

difference, however, and is reflected in the excessive mortality rate in this group of patients, 80 to 90 per cent before establishment of the Renal Insufficiency Center. After the center was organized and the artificial kidney put into operation the over-all mortality rate was still 53 per cent, the majority of deaths being attributable to complications of the original wounds. Figures for the mortality rate of acute renal failure in civilian practice vary widely. In a series of eighty-five cases of acute renal failure at the Peter Bent Brigham Hospital the over-all mortality rate was 48 per cent.[10] It is to be emphasized that many of these patients were problem cases, sometimes referred *in extremis* from other hospitals. In the only other large civilian series reported there was an over-all mortality rate of 31 per cent in sixty-four cases.[18] Comparison of these civilian figures with those obtained in the treatment of military casualties, such as presented in this report, offers many difficulties.

The striking feature of the patients with post-traumatic renal insufficiency here described was the rapidity with which chemical and clinical indications of uremia and potassium intoxication developed, reflecting the marked catabolic response to injury, infection and the presence of ischemic or devitalized tissue. This accelerated accumulation of nitrogenous waste products and extracellular potassium documented in the accompanying paper[6] occurred despite intensive medical treatment, the use of exchange resins, attempts to control infection with antibiotics and surgery, and early removal of devitalized tissue by débridement or amputation. Before establishment of the Renal Insufficiency Center the average survival time after wounding of patients who died with acute renal failure was only 6.8 days. The artificial kidney was effective in bringing about both chemical and clinical improvement but had to be used repeatedly in many patients. The average survival time of fatal cases was almost doubled (12.4 days) in those patients treated with the artificial kidney and extended to a period usually sufficient for diuresis to begin, except in the cases with severest renal damage.

Following the establishment of the Renal Insufficiency Center, and with the use of the artificial kidney, there was a fall in the over-all mortality rate from post-traumatic renal insufficiency of about 30 to 35 per cent (from 80 per cent to 53 per cent). Statistically this is not a very impressive reduction but there were a number of patients who seemed to survive because of the use of the artificial kidney and other measures. The limiting factor in survival in the present series of patients seemed to be the severity of the attending wounds. Because of this it is believed that the mortality rate accompanying acute renal failure in military casualties will be lowered below 50 per cent only with great difficulty and primarily through advances in the surgical care of the wounded.

The metabolic characteristics of the patients described here are not peculiar to battle casualties but are found in severely traumatized patients in any setting, civilian or military. Experience with the relatively benign nature of acute renal failure in uninjured and uninfected patients should not be misapplied to those who have developed renal insufficiency in the course of extensive surgical or accidental trauma.

SUMMARY

1. The management of fifty-one patients with post-traumatic renal insufficiency included fluid restriction, attempts to maintain caloric intake, use of cation exchange resins, the treatment of anemia and electrolyte disturbances and the use of a Brigham-Kolff artificial kidney. Interval surgical care of these patients was of great importance not only because of the severity of their wounds but particularly because of the necessity for removing necrotic and infected tissue in patients with renal failure.

2. Dialysis with the artificial kidney was carried out seventy-two times in thirty-one patients of this series. It was effective in restoring clinical and chemical abnormalities toward normal and seemed to contribute to the reduction in mortality in this group of patients.

3. The mortality rate accompanying acute renal failure in military casualties in Korea was approximately 80 to 90 per cent, similar to the mortality rate during World War II. After establishment of a Renal Insufficiency Center and with the use of a Brigham-Kolff type artificial kidney, the over-all mortality rate in the fifty-one patients was 53 per cent.

4. The limiting factor in survival for most military patients with acute renal failure is the extent of the underlying wounds with attending infection and impaired wound healing.

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REFERENCES

1. Thorn, G. W. Treatment of renal insufficiency. *J. Urol.*, 59: 119, 1948.
2. Strauss, M. B. Acute renal insufficiency due to lower nephron nephrosis. *New England J. Med.*, 239: 693, 1948.
3. Merrill, J. P. Medical progress: the artificial kidney. *New England J. Med.*, 246: 17, 1952.
4. Grollman, A., Turner, L. B. and McLean, J. A. Intermittent peritoneal lavage in nephrectomized dogs and its application to the human being. *Arch. Int. Med.*, 87: 379, 1951.
5. Twiss, E. E. and Kolff, W. J. Treatment of uremia by perfusion of an isolated intestinal loop. *J. A. M. A.*, 146: 1019, 1951.
6. Teschan, P., Post, R. S., Smith, L. H., Jr., Abernathy, R. S., Davis, J. H., Gray, D. M., Howard, J. M., Johnson, K. E., Klopp, E., Mundy, R. L., O'Meara, M. P. and Rush, B. F., Jr. Post-traumatic renal insufficiency in military casualties. I. Clinical characteristics. *Am. J. Med.*, 18: 172, 1955.
7. Muirhead, E. E. and Stirman, J. A. Acute progressive unrelenting renal failure. *Surgery*, 32: 43, 1952.
8. The Board for the Study of the Severely Wounded, The Physiologic Effects of Wounds, p. 122. Office of the Surgeon General, Dept. of the Army, 1952.
9. Murphy, W. P., Jr., Swan, R. C., Jr., Walter, C. W., Weller, J. M. and Merrill, J. P. Use of an artificial kidney. III. Current procedures in clinical hemodialysis. *J. Lab. & Clin. Med.*, 40: 436, 1952.
10. Swan, R. C. and Merrill, J. P. The clinical course of acute renal failure. *Medicine*, 32: 215, 1953.
11. Gamble, J. L. Water requirements of castaways. *Proc. Am. Philos. Soc.*, 88: 151, 1944.
12. Crosby, W. Personal communication.
13. Meroney, W. H. and Herndon, R. F. The management of acute renal insufficiency. *J. A. M. A.*, 155: 877, 1954.
14. Fenn, W. O. The role of potassium in physiological processes. *Physiol. Rev.*, 20: 377, 1940.
15. Johnson, K. E., Teschan, P. E. and Post, R. S. Cation exchange resins for control of hyperkalemia in patients with post-traumatic renal insufficiency. (In preparation.)
16. Moots, M. F. Acute anuric uremia. *U. S. Armed Forces M. J.*, 3: 1041, 1952.
17. Luetscher, J. A., Jr. and Blackman, S. S., Jr. Severe injury to kidneys and brain following sulfathiazole administration: high serum sodium and chloride levels and persistent cerebral damage. *Ann. Int. Med.*, 23: 741, 1943.
18. Legrain, H. Nephrites Aigues Anuriques. Paris, 1951. G. Doin et Cie.

Clinical Management of the Anuric Patient*

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DESPITE recent advances in the management of anuric and oliguric patients (Strauss,[1] Friedberg[2] and others), misconceptions regarding basic management persist in the literature and in practice. Thus a widely accepted dictum advises administration to such patients of a quantity of fluid equal to that lost in urine, vomitus and stool, plus 1,000 cc. daily as the estimated insensible loss. As a result of our experience with acutely oliguric patients we believe that such replacement is excessive and in many instances will constitute a serious or even fatal excess. Particularly unsound, we believe, is the rule of thumb that vomitus should be replaced with an equal amount of normal saline solution. The cases presented in this paper suggest that the fluid and salt intake of such patients should be considerably less than that hitherto advocated; that such restriction will prevent fatal overhydration; that the patients will be relatively comfortable and without thirst during the oliguric phase; and that diuresis will occur as usual in from nine to sixteen days.

In reviewing the literature since 1944 we discovered no report of any patient who had received 1,000 cc. or less of fluid per day during the entire oliguric phase. Friedberg's cases, despite the fact that he advocated administration of only 500 cc. of sodium-free fluid daily, had been seriously overhydrated before he began to treat them, as had those reported by Kugel.[3] Thus their advocacy of "rigid" restriction of fluid and salt is open to the criticism that the restriction of fluid they imposed during the two or three days before diuresis in their patients did not actually influence the course of the disease.

We consider that a correct regimen for the management of anuria consists almost entirely in the oral administration of about 500 cc. of 20 per cent lactose solution daily. Such a basic intake during the phase of oliguria supplies the 100 gm. of carbohydrate shown by Gamble[4] to provide maximal protein-sparing effect. In addition, because of its bland sweetness, lactose solution is not likely to prove nauseating.

We have found that frequent bedside evaluation, essentially without laboratory aids, will usually suffice to determine whether the daily intake should be more or less than 500 cc. Thirst, turgor of tissue, moisture of skin and mucosa, sweating, heart sounds, nausea, vomiting, rate of respiration, condition of the lungs and mental status are excellent and sufficient guides in a patient who is, in effect, a "closed system" with regard to the excretion of water and salt.

There is little knowledge concerning the amount of insensible loss of water during illness. The loss varies widely depending on environmental humidity and temperature, fever, respiratory rate and activity. Although ideally it would be desirable to replace the precisely determined insensible loss, no practical means of determination is available. Weighing the patient is rarely a useful method, particularly in the later phase of anuria, and scales ordinarily available are not sufficiently sensitive. The difficulty or impossibility of weighing vomitus and diarrheic stools, and of determining fluid lost by sweating introduces gross uncertainty in the interpretation of changes in weight.

Frequent and accurate determinations of blood volume were performed in one of our cases† and would appear to be invaluable in determining the patient's state of hydration. Radioisotope laboratories are not widely available, however, and older methods of determination are not sufficiently accurate. Moreover, unless blood volume is measured frequently and accurately, its determination is of little assistance in the physician's hour-to-hour decision as to how much fluid to administer. In our experience

† Blood volume levels in Case III were performed by Lt. Charles Foster, M.C., of the Radioisotope Laboratory, U. S. Naval Hospital, St. Albans, N. Y., using radioactive iodinated human serum albumin according to his modification of the technic of Aust et al.[5]

* The opinions expressed in this paper are those of the authors and do not necessarily represent the views of the Bureau of Medicine and Surgery, United States Navy.

the determinations served only in retrospect to assure us that we had been treating our patients correctly. They were of little practical help in determining future courses of action.

There has been considerable emphasis on the desirability of maintaining "normal" levels of plasma electrolytes in oliguric patients. Abnormal levels of chloride and bicarbonate have been particularly subject to therapeutic attack. Since administration of any corrective substance usually entails the use of sodium salts, the end result may be disastrous. We believe that the depression of chloride and CO_2 ions observed in these cases is adaptive, and not only benign but also necessary. Although our patients exhibited uniform reduction of Cl and HCO_3 we did not manipulate that alteration. Hyperkalemia, the usual cause of death in irreversible lesions, did not reach threatening levels or manifest itself clinically in our cases. Strauss has stressed the fact that in reversible lesions recovery usually occurs before hyperkalemia reaches fatal concentration.

CASE REPORTS

CASE 1. J. S., a twenty-three year old man, was admitted to the hospital on November 25, 1951, complaining of abdominal pain and of nausea and vomiting of one day's duration. A diagnosis of acute appendicitis was made and appendectomy was performed. The patient's immediate postoperative condition was satisfactory. The appendix was histologically normal. During the following days he remained nauseated, continued to vomit and accepted little of his prescribed diet. He received no parenteral fluids. Catheterization on November 26th yielded 220 cc. of urine. From that time until November 29th no urinary output was observed. On November 29th the patient stated that he had not voided for thirty-six hours. Catheterization obtained no urine.

Shortly thereafter a history of significant exposure to carbon tetrachloride was obtained. On Thanksgiving Day the man had drunk copiously of beer, whiskey and wine. The following morning, in spite of headache and dizziness, he had cleaned machinery with carbon tetrachloride. Later that day, in addition to dizziness, progressive nausea and vomiting developed. The next day, when the nausea increased and abdominal pain supervened, he entered the hospital.

Physical examination on November 29th disclosed an apathetic and obviously ill young man. His blood pressure was 160/100. Other vital signs were normal. There were moist rales at the bases of both lungs. Severe abdominal tenderness precluded palpation of the liver. The surgical incision appeared to be healing. There was no peripheral edema. Scleral icterus was not present. The blood urea nitrogen was 112 mg. per cent. A small amount of urine obtained by catheterization was cloudy and contained albumin, as well as many casts and red and white blood cells.

For four days the patient's daily intake was restricted to 500 cc. of 20 per cent lactose solution in 30 cc. increments when he desired to drink. Despite restriction of fluids the patient voided 135 cc. of urine the first day and steadily increased his output to 1,700 cc. in the fifth day, the twelfth day after exposure to carbon tetrachloride. In spite of the marked restriction of fluid intake he was not thirsty and always seemed to be comfortable. Turgor of tissue and hydration of the mucosal surfaces were normal. Because moist rales and hypertension persisted, and the venous pressure in the antecubital vein was 290 mm. of water, the patient was digitalized with lanatoside C. The blood urea nitrogen rose to a maximal level of 220 mg. per cent. Serum electrolyte values and a blood pH of 7.1 bespoke the severity of the acidosis. The serum potassium rose to 6.5 mEq. per liter. Tests of liver function were unremarkable. The blood creatinine rose to 18.6 mg. per cent. The blood calcium was consistently low. With the onset of diuresis the patient's intake was increased each day to approximate his output of the previous day. On the fourteenth day following exposure he was allowed food as desired, and received in addition an intravenous infusion of 1 L. of 5 per cent glucose in normal saline solution. During the following days he improved rapidly. The excretion of urine returned to relatively normal levels and the blood urea nitrogen steadily declined. By December 13th, the twenty-first day after exposure, the blood pressure had become normal, the blood urea nitrogen was 29 mg. per cent and the patient was ambulatory. By March 27th the specific gravity of the urine in random specimens ranged around 1.022. In late January epigastric pain developed. X-rays disclosed an active duodenal ulcer. The usual measures of therapy affected symptomatic control and regression of the radiographic abnormalities. His

convalescence was not otherwise remarkable. For additional data see Figure 1.

CASE II. On New Year's day 1952, N. A. W., a twenty-eight year old machinist, cleaned machinery with carbon tetrachloride in a closed room. Although he had been drunk the night before, he felt well on the day of exposure. The following day he became nauseated, vomited frequently and had a temperature of 102°F. He became icteric on the second day and signs of a mild upper respiratory infection developed for which he received an injection of penicillin. During the next two days he remained nauseated and inappetent and was unable to retain food or water. On the fourth day of illness he was admitted to the hospital with a diagnosis of infectious hepatitis.

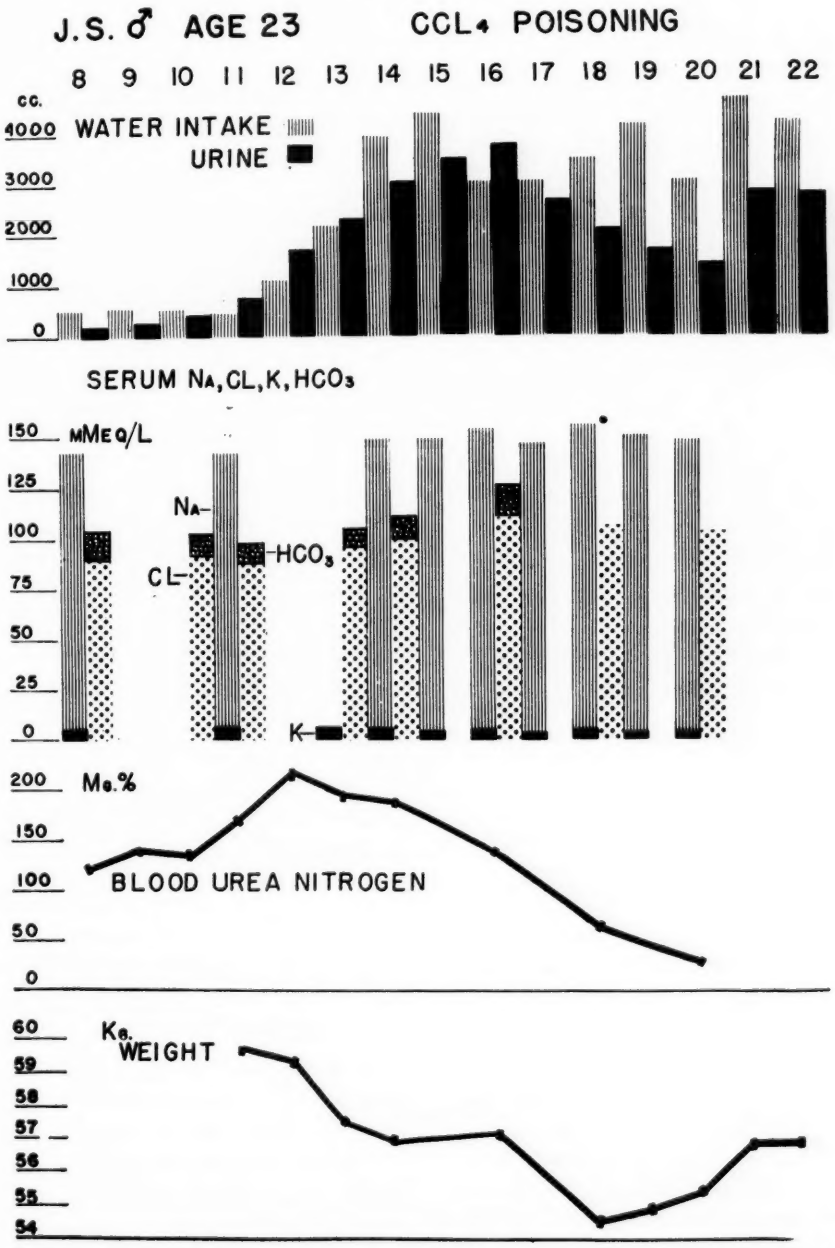

FIG. 1. Case I. Graphic representation of fluid balance, serum electrolytes, blood urea nitrogen and body weight.

Initial physical examination disclosed a dehydrated, uncomfortable young man with moderate scleral icterus. There was slight oropharyngeal injection. The blood pressure was 140/98. No spider angiomas were present. The

liver was not enlarged or tender. Urinalysis disclosed the specific gravity to be 1.020. There was four-plus albuminuria. Ten to fifteen white blood cells and eight red blood cells per high power field were seen in the centrifuged urine sediment. A hemogram was not remarkable. Blood electrolyte measurements were not immediately performed. The blood urea nitrogen was 73 mg. per cent.

A brief period of observation confirmed the early suspicion that the patient was oliguric. Intravenous fluids initially ordered were discontinued after the patient had received 1 L. of 5 per cent glucose in normal saline solution. Thereafter the fluid intake was severely restricted. During the following week the patient received 20 per cent lactose solution orally in 40 to 50 cc. increments at frequent intervals. His total daily intake ranged from a low of 15 cc. during the fifth day of his illness to a high of 1,080 cc. in the thirteenth day. During that period the urinary output rose from 50 cc. on the fifth hospital day to 330 cc. on the thirteenth day. No other fluid or food was given, except that water was used occasionally instead of lactose solution. The patient appeared to be relatively comfortable, did not complain of thirst and, although he was occasionally nauseated, he did not vomit during the period of oliguria. The level of blood urea nitrogen steadily rose to 208 mg. per cent on the fifteenth day. Other plasma electrolyte levels included a serum potassium level of 6.2 mEq. per liter, and a bicarbonate level of 17.9 mEq. per liter. The sodium level remained essentially unchanged but the chloride level dropped to 78.6 mEq. per liter. During the early stages of diuresis the patient's course was marked by continuing hypertension of the order of 170/110 and profound lethargy. He vomited occasionally but in small amounts and received half-liter infusions of glucose to supplement his oral intake. On the sixteenth day he vomited 300 cc. of grossly sanguineous material. During the next five days frequent hematemesis and melena continued for which repeated blood transfusions were given. A regimen of frequent small amounts of milk, sedatives and antispasmodic drugs was tried with indifferent success. Bilateral parotitis developed which was treated successfully with x-irradiation. By the twenty-second day of illness the patient's daily urinary output exceeded 5,000 cc. Melena and hematemesis had ceased, and the blood urea nitrogen had regressed. He was able to tolerate a soft diet. Fluids were given on demand without urging and parenteral administration was used only when necessary to prevent clinical dehydration. By the thirty-second day all laboratory values had returned to normal and the blood pressure had fallen to normal. The specific gravity of the urine was 1.012. Four months after the onset of illness the patient had no complaints. Physical examination and indicated laboratory studies were uniformly normal except that gastrointestinal x-ray disclosed evidence of duodenal deformity. (Fig. 2.)

Case III. Mrs. L. J., a thirty-seven year old primigravida at approximately three months, entered the hospital January 5, 1953, because of intermittent slight bleeding from the vagina of three week's duration. She had no other complaints. She was a slender, active woman who, except for slight pallor, appeared well. Her vital signs were normal. The fundus of the uterus was palpated 6 cm. below the umbilicus. The urine was normal. The hemoglobin was 11.5 gm. per cent.

Although the patient remained in bed, the following morning she began to have uterine contractions and six hours later passed a normal three and a half month fetus. Her loss of blood was estimated at about 250 cc. However, because she appeared pale and listless after delivery, a blood transfusion was started the evening of January 9th. Within a few minutes the patient experienced pain in the back and epigastrium, a severe rigor, urticaria of the face and eyelids, rise in temperature to 104°F., and nausea and vomiting. She passed a large liquid stool. The transfusion was stopped. Investigation disclosed that the patient, whose blood was Rh-positive, Type O, had received about 30 cc. of Rh-positive, Type A blood.

The acute symptoms subsided within an hour. The following morning her temperature was normal. Her blood pressure remained about 110/70. Although the urine obtained by catheterization two and a half hours after the transfusion was normal, that obtained the following morning was cloudy and dark, with a specific gravity of 1.020. It contained 150 mg. per cent of albumin, granular casts and white and red blood cells. Blood drawn twelve hours after transfusion showed hemolysis. The serum bilirubin was 0.85 mg. per cent. Because of the possibility of serious renal damage, during the patient's first post-transfusion day her intake of fluid was limited to 1,200 cc. An indwelling

catheter insured that all urine was collected. Thereafter she received not more than 1,000 cc. of fluid daily. Her actual intake was dictated by thirst. During the first nine days of oliguria her daily intake, which was entirely oral, consisted of water and tea with approximately

fourth week following the onset of illness showed good renal function and normal anatomy. At the end of three and a half months a urea clearance was 85 per cent of the average normal value. A dilution and concentration test disclosed specific gravities of 1.007 and 1.022. (Fig. 3.)

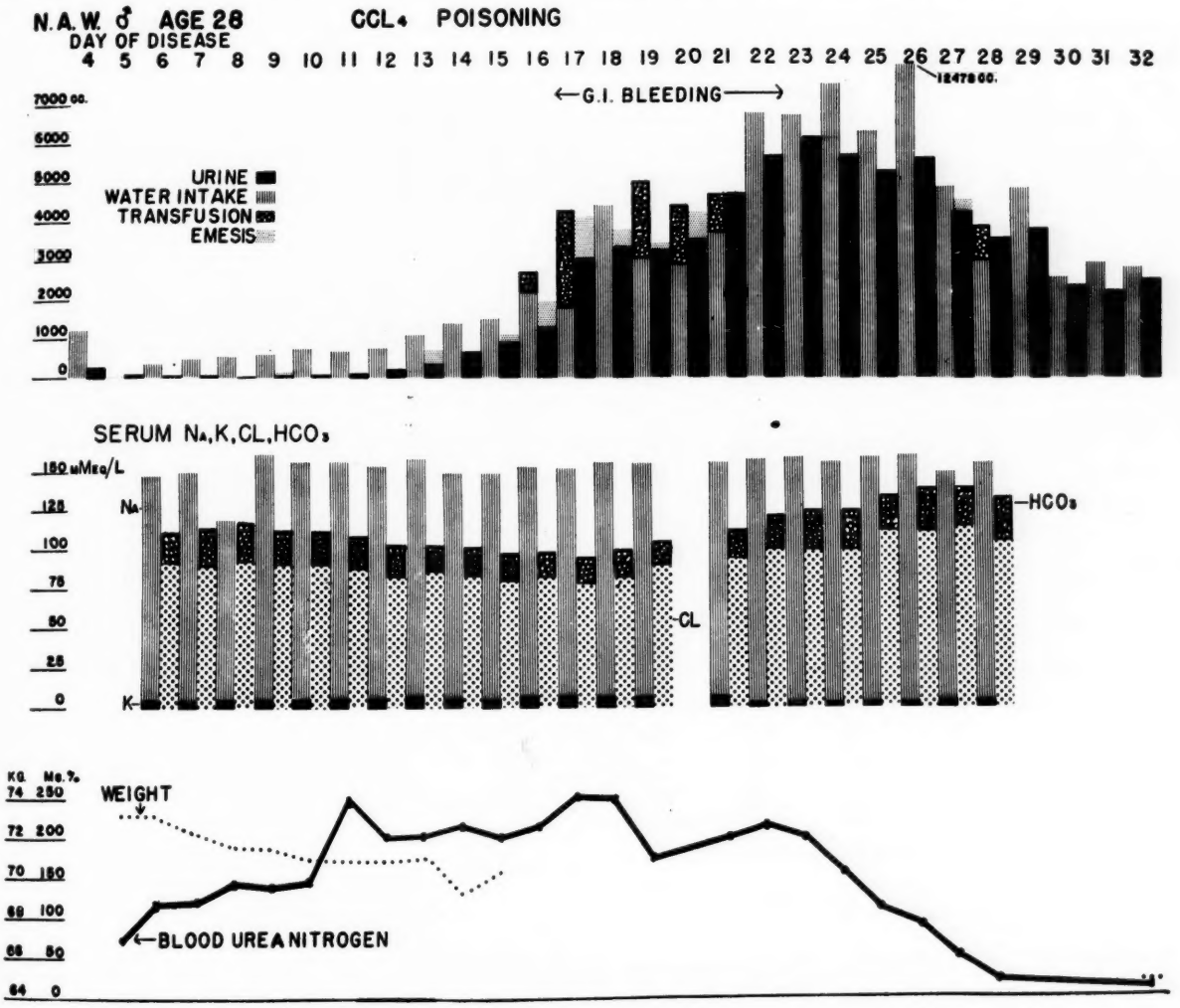

FIG. 2. Case II. Fluid balance, serum electrolyte values, blood urea nitrogen level and weight.

100 gm. of lactose. She had few complaints and appeared alert and comfortable except for one occasion of brief nausea. In spite of the strict limitation of fluids her hydration remained normal as evidenced by clinical signs. Daily determinations of blood volume confirmed those clinical impressions. One day after the onset of diuresis, the tenth day, rice was added to the diet. Thereafter the patient selected her own diet from the general menu. Six electrocardiograms taken during the period of oliguria were normal. A few days after diuresis began the patient's appetite improved and her convalescence proceeded rapidly. Excretory urograms made in the

CASE IV. B. J. K., a twenty year old primigravida, was first seen in the prenatal clinic during the twelfth week of her pregnancy in January, 1953. The predicted date of delivery was July 26th. Except that she appeared to be apprehensive, her course was uneventful until June 19th when she entered the hospital because of the onset of vaginal bleeding and labor four hours previously. She was terrified. The initial examination disclosed a blood pressure of 120/80 and was otherwise negative. Although a marginal placenta was suspected, since the bleeding was slight and labor was progressing satisfactorily, pelvic examination was not performed,

Saddle block anesthesia was instituted in the second stage of labor. During that phase her blood pressure suddenly rose to 150/100, severe pulmonary edema ensued and her pulse increased to 168 per minute. She was digitalized with lanatoside C and received aminophyllin, thirty-six hours. During the twenty-four hours following delivery her total urinary output, collected by indwelling catheter, was 120 cc. despite a total intake of 3,450 cc. During the second twenty-four hours the output was only 160 cc.; the intake 2,450 cc. Her urine at that

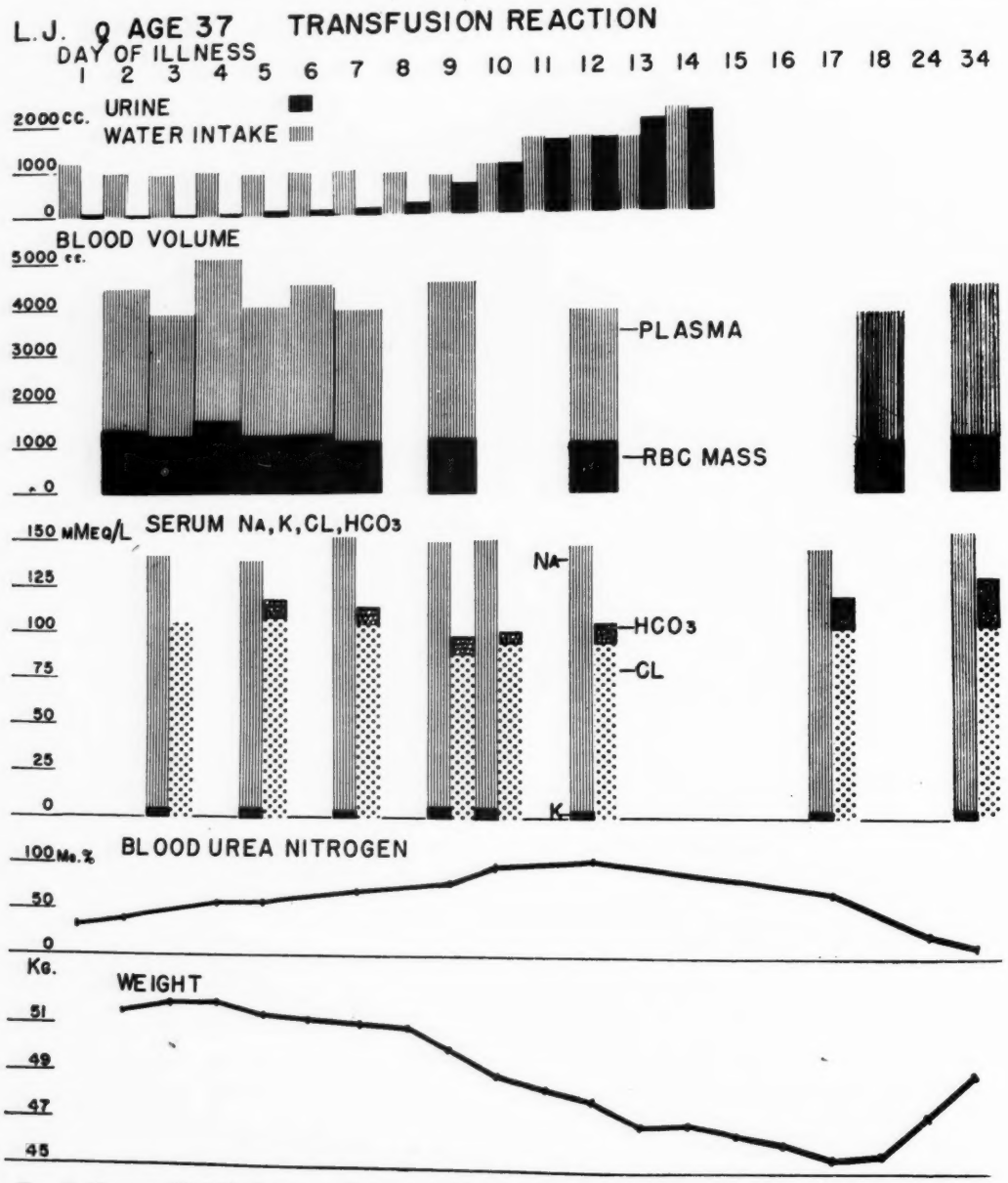

FIG. 3. Case III. Fluid balance, radioisotopic blood volume determinations, serum electrolyte values, blood urea nitrogen level and weight.

with some improvement. Immediately after the spontaneous delivery of a dead seven and a half month male infant there was massive blood loss. Severe shock ensued and persisted for five hours in spite of immediate transfusion of 1,000 cc. of type-specific, compatible whole blood. The blood pressure persisted around 85/60 for time was reddish and cloudy, with a specific gravity of 1.018, and contained 100 mg. per cent of albumin and many red and white blood cells and granular casts. The second day, when it had become evident that the patient had sustained serious renal damage, she was given a basic intake of 100 gm. of lactose. Since in south-

eastern Texas during that June and July the weather was exceedingly hot and the patient exhibited obvious sweating, she was permitted to drink water or tea sweetened with lactose as her thirst dictated. Figure 4 demonstrates that in spite of the heat and sweating she was eye grounds were normal. That day moderate carpopedal spasm and tetanic contractions of the right arm developed which were relieved by the infusion of 15 cc. of 10 per cent calcium gluconate solution on two occasions. Thereafter her convalescence was uneventful until the seven-

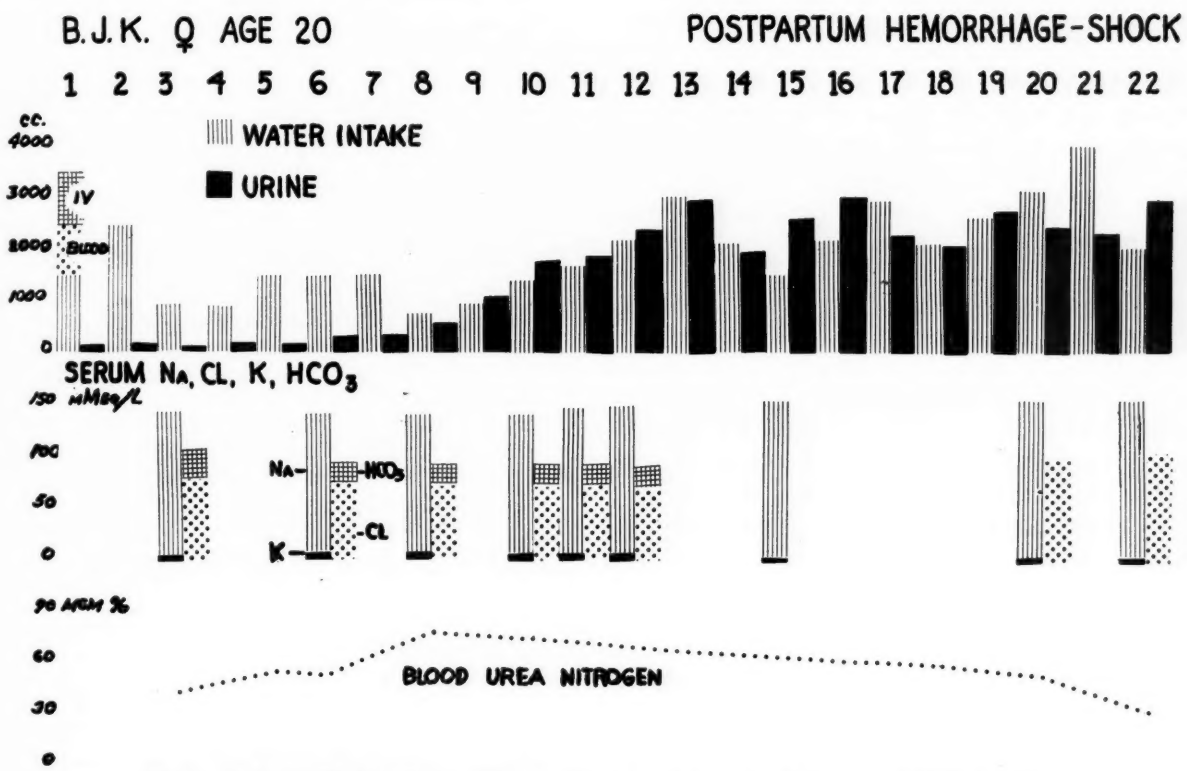

FIG. 4. Case IV. Fluid balance, serum electrolyte values and blood urea nitrogen level.

satisfied with less than 1,000 cc. of liquid a day during the first two days of that regimen; 1,500 cc. the following three days, and less than 1,000 cc. in the sixth and seventh days when the output of urine first exceeded 500 cc. per day. The blood urea nitrogen rose to a maximum of 77 mg. per cent on the fifth day and slowly fell. Although it was still 35 mg. per cent on the twenty-second day of her illness, the patient left the hospital against advice, considering herself well. The plasma chloride lev l was consistently low until the twentieth day. Although the elevation of plasma potassium to a maximum of 7.5 mEq. per liter was reported, there was no clinical evidence of hyperkalemia. During the oliguric phase the patient remained comfortable and cheerful. Her hydration as judged by clinical evidence was always satisfactory.

On the ninth day, when diuresis was definitely established, the patient complained of blurring of vision and she was briefly nauseated. The teenth day when cystitis due to Aerobacter aerogenes developed. The infection caused a low grade fever for four days but responded to treatment with chloramphenicol.

During the second and third days of the illness electrocardiograms showed inversion of T-1 and T-AVL which thereafter became erect and so remained. After the initial concentration of 1.018 the urine specific gravity remained fixed between 1.007 and 1.011 for thirty-five days. During the first week there was minimal albuminuria and cylindruria.

When the patient was seen in the outpatient clinic thirty-two days after the onset of her illness she had no significant complaints. The examination was not remarkable except for a small, bleeding laceration of the cervix and a red blood count of 3.3 million per cu. mm. The blood urea nitrogen was normal. A Fishberg concentration test on the forty-eighth day showed maximal specific gravity of 1.025. The

blood count, urinalysis and blood urea nitrogen levels were normal. (Fig. 4.)

SUMMARY AND CONCLUSIONS

1. Four cases of acute and severe oliguria are presented. Two resulted from carbon tetrachloride intoxication, one followed incompatible transfusion and one followed shock associated with postpartum hemorrhage. Each patient recovered under treatment which consisted, during the oliguric phase, of a minimal oral intake of lactose solution. In essence, the intake of fluid was dictated by the patient's thirst.

2. No attempt was made to replace or alter electrolytes during the period of oliguria. Despite restriction of fluids and food to a degree and for periods of time hitherto not reported, the patients progressed to diuresis in nine, ten, twelve and sixteen days, respectively. Subsequent studies disclosed apparent recovery of the renal lesions.

3. The extremely low fluid intake maintained adequate hydration as evidenced by clinical evaluation. The validity of those evaluations was confirmed in one patient by repeated blood volume determinations. It is noteworthy that the regimen was successful under extremely variable environmental conditions.

4. Good management of the oliguric patient can be carried out on the basis of bedside clinical observation; if necessary, without the support of elaborate laboratory aids.

REFERENCES

1. Strauss, M. B. Acute renal insufficiency due to lower-nephron nephrosis. *New England J. Med.*, 239: 693, 1948.
2. Friedberg, C. K. Congestive heart failure of renal origin. Pathogenesis and treatment in four cases of carbon tetrachloride nephrosis. *Am. J. Med.*, 9: 164, 1950.
3. Kugel, V. H. Management of acute toxic nephrosis. *Am. J. Med.*, 3: 188, 1947.
4. Gamble, J. L. Physiologic information gained from studies on the life raft ration. *Harvey Lect.*, pp. 247–273, 1946–47.
5. Aust, J. B. et al. A rapid method for clinical total blood volume determination using radioactive iodinated serum albumin (RIHSA). *Proc. Soc. Exper. Biol. & Med.*, 77: 514, 1951.

Cystic Disease of the Kidneys*

A Study of Dynamics and Chemical Composition of Cyst Fluid

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INVESTIGATION of the physiologic derangements of congenital structural abnormalities is one of the requisites to a thorough understanding of the nature and therapy of these diseases. In recent years fundamental research has furthered knowledge of a variety of congenital anomalies. This progress, perhaps best illustrated in the case of congenital cardiovascular disorders, has not been shared in appreciably by polycystic disease of the kidneys, a malady which is frequently associated with slowly progressive renal failure culminating ultimately in death. The present report represents an attempt to explore the fundamental nature of the polycystic kidney through *in vivo* physiologic experiments. The studies to be described were performed in patients with polycystic disease of the kidneys and patients with simple renal cysts at the time of surgical exposure of the involved organs.

METHODS

Data were obtained from the study of five adults with polycystic renal disease (six individual kidneys), one infant with polycystic renal disease and four adults with simple renal cysts (five individual kidneys). Case number, diagnosis and age of all patients are included in Table I. The studies on the adult polycystic kidneys are included in Cases I through VI. Two of these experiments (Cases II and VI) were performed at two-month intervals on separate kidneys of the same patient. The range of ages for the adult polycystic patients was from twenty-three to forty years. The infant patient, referred to as Case VII, was twenty-one months old at the time of study. Cases VIII through XI constitute the group with simple renal cysts. The ages in these patients ranged from forty-two to sixty-eight years. Description of the simple cysts is included in Table I.

TABLE I
CASE MATERIAL

CASE NO.	DIAGNOSIS	AGE	COMMENT
I	PCD*	30	
II	PCD	40	Right kidney
III	PCD	31	
IV	PCD	23	
V	PCD	34	
VI	PCD	40	Left kidney of Case II
VII	PCD	21 mo	Large bilateral polycystic kidneys; essentially asymptomatic at the time of surgery.
VIII	S.C.†	54	Solitary cyst (80 ml. of fluid).
IX	S.C.	53	Two noncommunicating cysts; one superficial (10 ml. of fluid) and one deep (20 ml. of fluid).
X	S.C.	42	Solitary cyst containing 125 ml. of fluid surrounded by 5 noncommunicating cysts containing from 0.5 ml. to 15 ml. of fluid.
XI	S.C.	68	Bilateral solitary cysts; right kidney sampled at surgery (1000 ml. of fluid); left kidney sampled at autopsy two days later (125 ml. of fluid).

* PCD = polycystic disease.
† SC = simple cysts; the volumes quoted for simple cysts are approximations.

Surgical exposure was accomplished through a conventional lumbar approach and experi-

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ments were carried out without impinging on the renal pedicle. All kidneys, with the exception of one postmortem study on Case XI, were studied *in situ* at the time of laparotomy. Immediately after exposure, fluid was aspirated from separate cysts in the polycystic kidneys and from a solitary cyst in the simple cystic kidneys. The initial samples served as blanks for inulin and PAH studies. Subsequent to the initial sampling a single dose of inulin and in some cases PAH was administered intravenously.* In one patient (Case IV) the single injection of inulin (40 cc. of a 10 per cent solution) was administered as a priming dose and was followed by a sustaining infusion of inulin (30 mg./min.), delivered by a constant infusion pump.† At timed intervals after drug administration single samples were taken from different cysts in the polycystic kidneys and serial samples were taken from single cysts in the kidneys containing simple cysts. In the patient receiving the constant infusion two cysts sampled before inulin infusion were aspirated a second time after the infusion of inulin. In the polycystic studies cysts were aspirated at various levels in the kidneys. Those cysts, referred to in the text as *superficial*, presented at the capsular surface of the kidney; whereas those cysts referred to as *deep* were situated at various levels beneath the surface of the kidney. The latter group were sampled by inserting a needle into the renal parenchyma until a pocket of fluid was reached. In the majority of instances the polycystic cysts were aspirated as completely as possible; however, because of mechanical factors, it could never be assumed that all of the fluid in any cyst was obtained. In several cases urine was collected throughout the procedure by inlying bladder or ureteral catheters.

Heparinized venous blood samples (0.1 ml. heparin/10 ml. blood) were drawn during the control period and on one or more occasions after drug administration. Plasma, separated by centrifugation, and cyst fluid samples were analyzed for inulin, PAH, creatinine, sodium, potassium, chloride, freezing point depression and protein. The number of separate analyses performed on any individual cyst fluid sample was limited by the volume of fluid obtained.

* The dose of inulin was calculated to produce a plasma concentration of 40 to 60 mg. per cent in an assumed volume of distribution of 18 per cent body weight. PAH was administered empirically in amounts varying from 7 to 10 ml. of a 20 per cent solution.

† Bowman pump; Process and Instruments, Brooklyn, N. Y.

Inulin was determined by a modification of the method of Roe et al.;[1] PAH by the method of Smith et al.;[2] creatinine by the method of Bonsnes and Taussky;[3] chloride by the method of Van Slyke and Hiller;[4] sodium and potassium on a Baird internally compensated flame photometer; freezing point by the method of Wesson[5] using NaCl solutions as standards, and protein by the method of Phillips et al.[6]

RESULTS

Inulin Studies

Adult Polycystic Kidneys. Composite data for the six experiments in this group are recorded in Table II. In all cases except one, at least two separate cysts were sampled prior to inulin injection. In Case VI one control sample was obtained. Cyst fluid (hereafter referred to as CF) inuloid blank levels approximated plasma blanks in four experiments, and in two (Cases II and III) CF blanks exceeded plasma blanks. In all studies, irrespective of the level of the CF blank, the concentration of inulin in the majority of CF samples obtained after inulin injection exceeded control values. Thus twenty-one of the twenty-eight postinjection samples were greater than control values from their respective kidneys. Results of a representative experiment are shown in Figure 1. The plasma inuloid blank was 1.4 mg. per cent and the blank values for two CF samples were 2.4 and 2.0 mg. per cent, respectively. Of seven postinjection CF samples five exceeded control values, ranging from 4.0 to 10.2 mg. per cent.

The observed concentrations of inulin did not appear to bear a fixed relationship to the depth of the cysts in the kidney. In Case I (Table II) the inuloid blank level was higher in the superficial cyst (cyst 1) than in the deep cyst (cyst 2). Moreover, postinjection values in all cases appeared to be essentially independent of the site of the parent cyst. Calculation of the total amounts of inuloid material in individual cysts (inulin concentration times CF volume) was not feasible due to the inexactness of CF volume measurements.

In Case IV two representative superficial cysts sampled during the control period were reaspirated thirty-nine and forty-one minutes, respectively, after the prime injection and initiation of a continuous infusion of inulin. Plasma inulin concentration was maintained at about 40 mg. per cent. Comparison of the post-

infusion values with control values demonstrated a definite increase in inulin concentrations in the fluid of both cysts. (Fig. 2.) It was not possible to determine the total amount of inulin entering either cyst during the timed intervals of study due again to inability to measure cyst fluid volumes with accuracy.

Infant Polycystic Kidney. The subject of this study was a twenty-one month old male with bilateral polycystic disease (Case VII). The studies were obtained at the time of operation on the right kidney. Inulin analyses were performed on samples from thirteen individual cysts. (Fig. 3.) Of the eleven samples examined after the

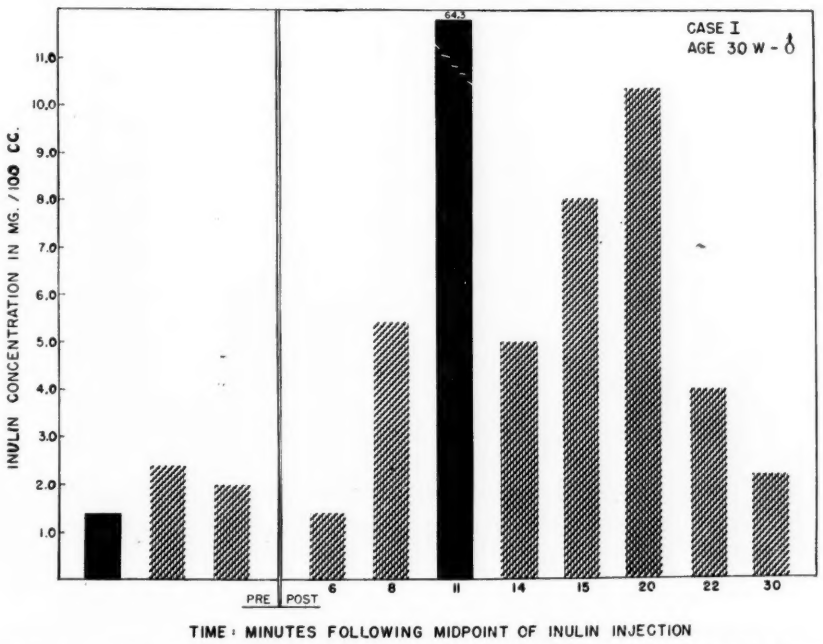

FIG. 1. Inulin concentration in cyst fluid before and after intravenous administration of inulin. Solid bars represent plasma values and cross-hatched bars represent individual cyst fluid values.

TABLE II

COMPOSITE INULIN DATA ON ADULT POLYCYSTIC KIDNEYS*

	CASE I			CASE II			CASE III			CASE IV			CASE V			CASE VI		
	TIME	INULIN		TIME	INULIN		TIME	INULIN		TIME	INULIN		TIME	INULIN		TIME	INULIN	
		Mg%	Mg%-BLANK		Mg%	Mg%-BLANK		Mg%	Mg%-BLANK		Mg%	Mg%-BLANK		Mg%	Mg%-BLANK		Mg%	Mg%-BLANK
PLASMA																		
1	0	1.4		0	1.8		0	1.2		0	2.0		0	2.2		0	2.4	
2	11	64.2	62.8	13	68.8	67.0	0	47.6	46.4	16	40.8	38.8	19	77.2	75.0	15	65.8	63.2
CYST FLUID																		
1	0	2.4		0	18.6		0	9.2		0	1.8		0	1.7		0	2.2	
2	0	2.0		0	21.6		0	4.4		0	2.0		0	1.9		3	5.6	3.4
3	6	1.4	—	11	29.0	8.9	5	12.0	2.8	0	2.4		14	1.9	0.1	4	5.6	3.4
4	8	5.4	3.2	12	41.2	21.1	8	12.8	3.6	30	20.6	18.5	19	14.1	12.3			
5	14	5.0	2.8	13	38.3	18.2	9	12.8	3.6	39	3.8	2.0	23	6.1	4.3			
6	15	8.0	5.8	23	16.3	—	12	8.4	—	41	4.6	2.6	28	38.0	36.2			
7	20	10.2	8.0	33	24.6	4.5	15	2.4	—									
8	22	4.0	1.8	45	19.8	—	19	47.7	38.5									
9	30	2.2	—	46	14.8	—												

* Time refers to minutes following the mid-point of inulin injection. In Case IV in which a constant infusion of inulin was delivered, time refers to minutes following the mid-point of priming injection. All 0 times refer to the control period. In Case III the inuloid blank value for cyst fluid was taken as 9.2 mg. per cent. In Cases I, II and V the two blank values were averaged. In Case IV cyst fluid samples 1 and 5 were obtained from a single cyst, and 2 and 6 from a single cyst. Sample 4 was compared to the average blank value.

intravenous injection of inulin, eight were found to approximate the inuloid blank values. It is of interest to note, however, that three individual samples were markedly in excess of blank levels. This observation will be discussed subsequently in greater detail.

were obtained from a solitary cyst before and at timed intervals after the intravenous injection of an amount of inulin approximately double that given to the adult polycystic cases (i.e., 100 ml. of a 10 per cent solution). The results of this study, shown in Figure 4, failed to reveal an

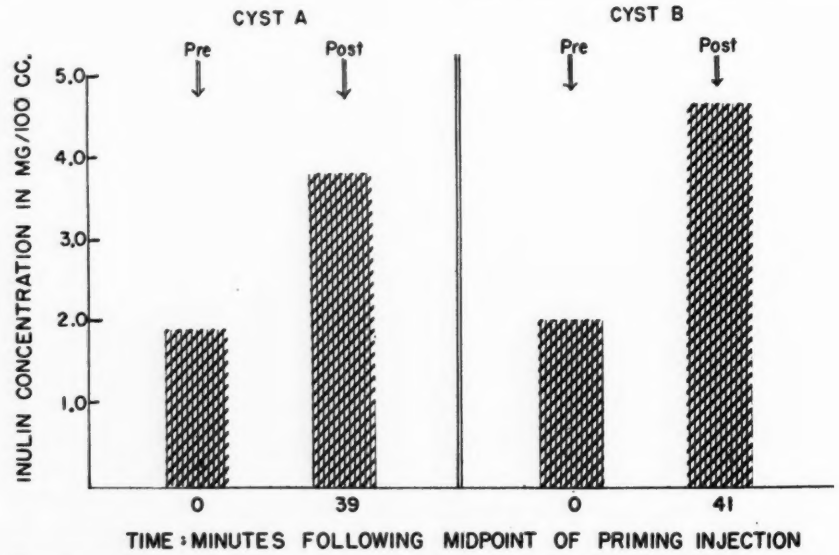

FIG. 2. Acute increase in cyst fluid inulin concentration during the continuous infusion of inulin.

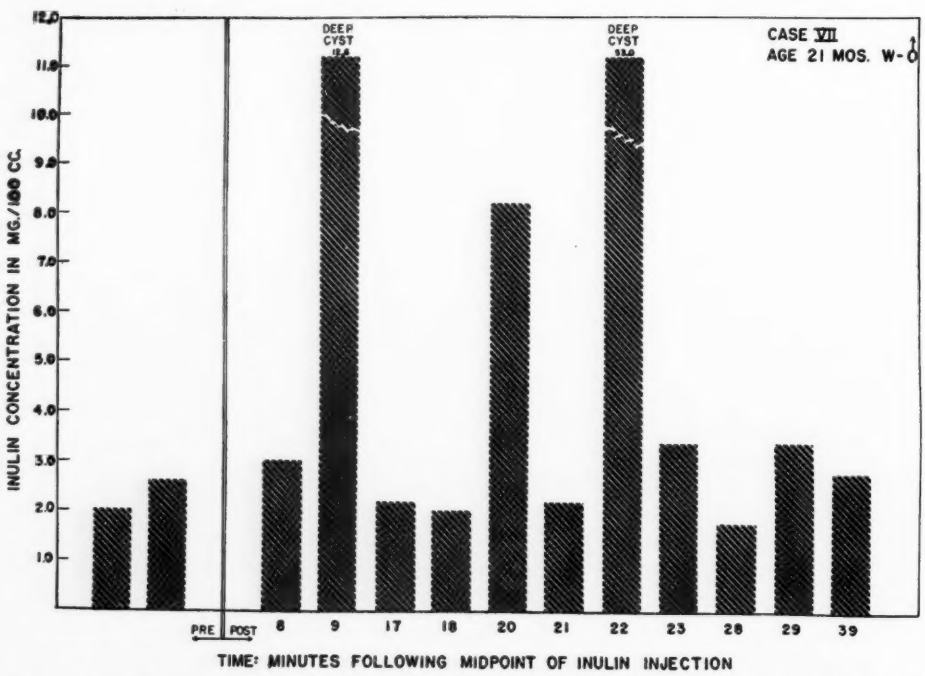

FIG. 3. Inulin concentration in cyst fluid before and after intravenous administration of inulin. Bars represent individual CF values.

Simple Cysts. Inulin studies were performed in three patients with simple cysts of the kidneys. CF inuloid blank levels approximated plasma blanks in each experiment. In Case VIII samples

appreciable increase in inulin concentration during the period of sampling although the plasma inulin concentration was recorded at 138 mg. per cent. The volume of fluid in this

cyst, however, was large (i.e., approximately 80 ml.), and the inability to demonstrate a rising concentration of inulin did not necessarily rule out the entrance of small amounts of this substance. In Case x a more critical study was provided. In addition to a large mother cyst, containing approximately 125 ml. of CF, a series of five small satellite cysts was sampled. The volume of fluid in the satellite cysts was of the same order of magnitude as that found in the typical polycystic cyst (i.e., from 0.5 to 15 ml.). The results of these studies are shown in Figure

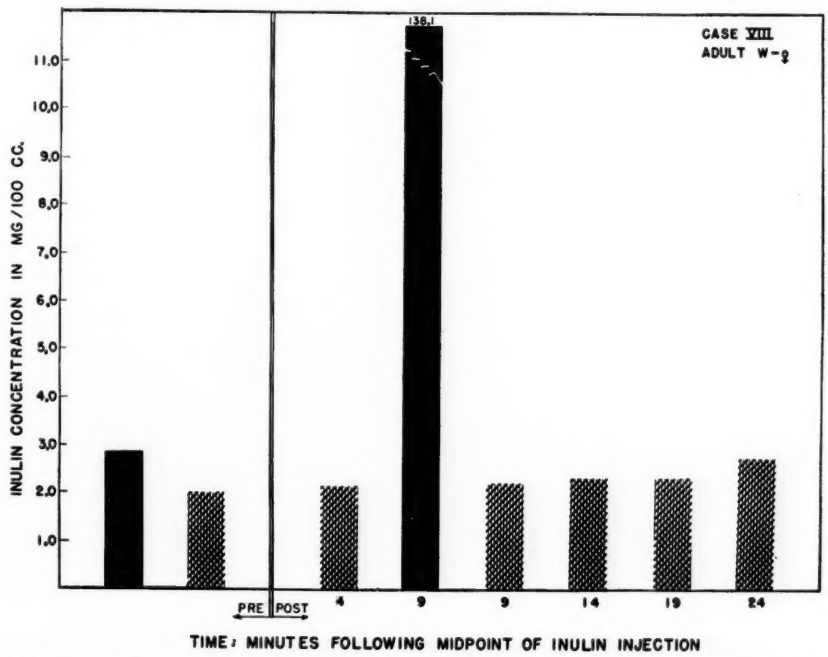

FIG. 4. Inulin concentration in solitary cyst fluid before and after intravenous administration of inulin. Solid bars represent plasma values. Cross-hatched bars represent serial samples from a single cyst.

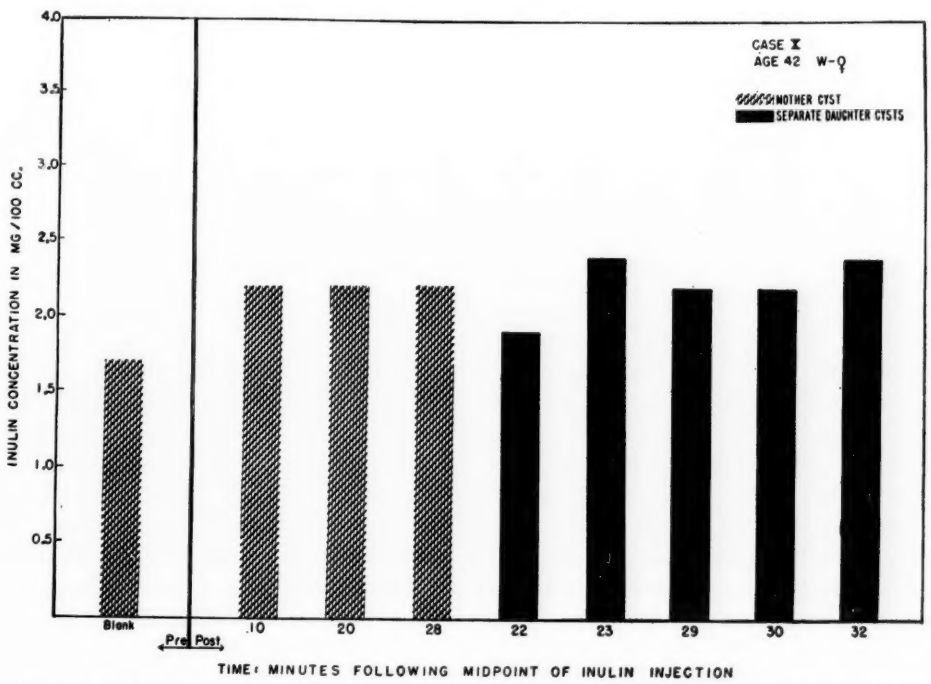

FIG. 5. Inulin concentration in cyst fluid before and after intravenous administration of inulin.

5. Inspection of the bar graph demonstrates the fact that no appreciable increase in inulin concentration, above the inuloid blank level, occurred in either the mother cyst or any of the daughter cysts during the thirty-two minute period of sampling. The results in Case IX were similar to the two foregoing studies. In this patient the plasma blank was 1.7 mg. per cent and the CF blank 1.8 mg. per cent. Identical values of 1.9 mg. per cent were recorded in two non-communicating simple cysts (one superficial and one deep), nineteen and twenty-nine minutes, respectively, after injection of 5 gm. of inulin.

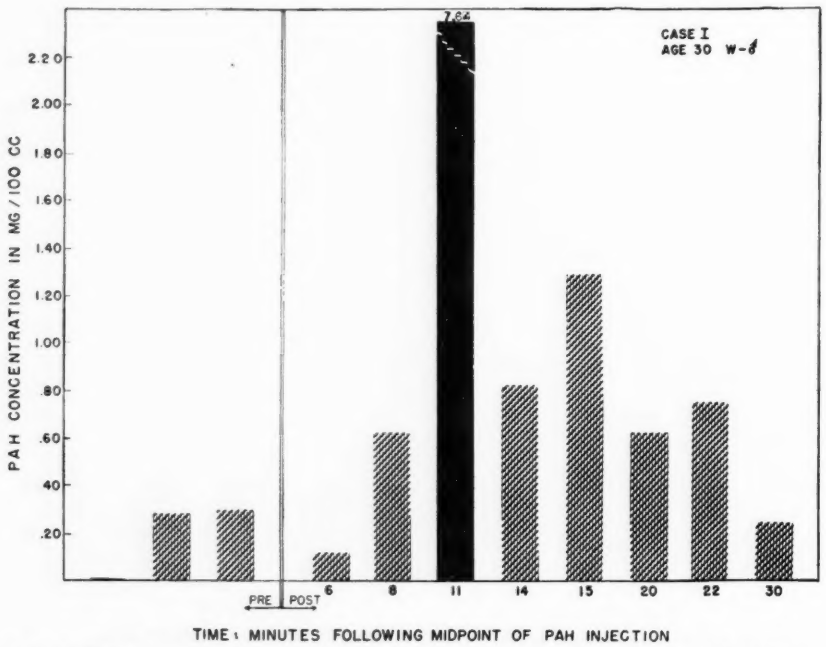

FIG. 6. PAH concentration in cyst fluid before and after intravenous administration of PAH. (See legend for Fig. 1.)

PAH Studies

Adult Polycystic Kidneys. PAH was administered intravenously in two adult patients with polycystic kidneys. The results were comparable to those observed in the inulin studies. Figure 6 shows the results of PAH injection in Case I. Although the CF blanks were somewhat greater than the plasma blank, PAH values in five of the seven postinjection CF samples exceeded the preinjection levels. In this experiment, as in the inulin studies, the concentration of PAH did not appear to be related to the site of the cyst in the kidney. In the second PAH study (Case II) the CF blank value for PAH exceeded the simultaneous plasma blank to a marked degree. This patient, as already noted, also had a high CF inuloid blank. Subsequent to PAH injection all four postinjection samples exceeded the control value. Data for both cases are summarized in Table III.

Simple Cysts. PAH was administered intravenously in two patients with simple renal cysts. (Table III.) Small amounts of PAH may have entered the cyst fluid in the postinjection period although the changes were of small magnitude.

Relationship between Inulin and PAH in the Same Polycystic Cysts

In many of the individual cyst fluid samples the volume of fluid obtained was not sufficient to allow simultaneous analyses for both inulin and PAH. In Case I, however, nine separate samples were analyzed for both substances. The results shown in Figure 7 indicate that the relationship of inulin and PAH to their respective CF blanks was roughly comparable in individual samples. Thus in two postinjection samples neither inulin nor PAH exceeded control values, whereas in the remaining five postinjection samples both inulin and PAH concentrations were greater than their respective blank levels.

TABLE III

COMPOSITE PAH DATA

	POLYCYSTIC CYSTS						SIMPLE CYSTS					
	CASE I			CASE II			CASE VIII			CASE IX		
	Time	PAH		Time	PAH		Time	PAH		Time	PAH	
		mg %	mg % – Blank		mg %	mg % – Blank		mg %	mg % – Blank		mg %	mg % – Blank
Plasma												
1	0	0.01		0	0.03		0	0.02		0	0.02	
2	11.0	7.64	7.63	12.5	7.65	7.62	25.0	4.35	4.33	7.0	21.2	21.2
Cyst Fluid												
1	0	0.29		0	1.47		0	0.02		0	0.01	
2	0	0.30		20.5	8.10	6.63	4.0	0.02		19.0	0.05	0.04
3	6.0	0.12		22.5	4.02	2.55	9.0	0.02		29.0	0.15	0.14
4	8.0	0.62	0.32	32.5	7.28	5.81	14.0	0.02				
5	14.0	0.82	0.52	44.5	3.87	2.40	19.0	0.03	0.03			
6	15.0	1.29	0.99				24.0	0.10	0.08			
7	20.0	0.62	0.32									
8	22.0	0.75	0.45									
9	30.0	0.25										

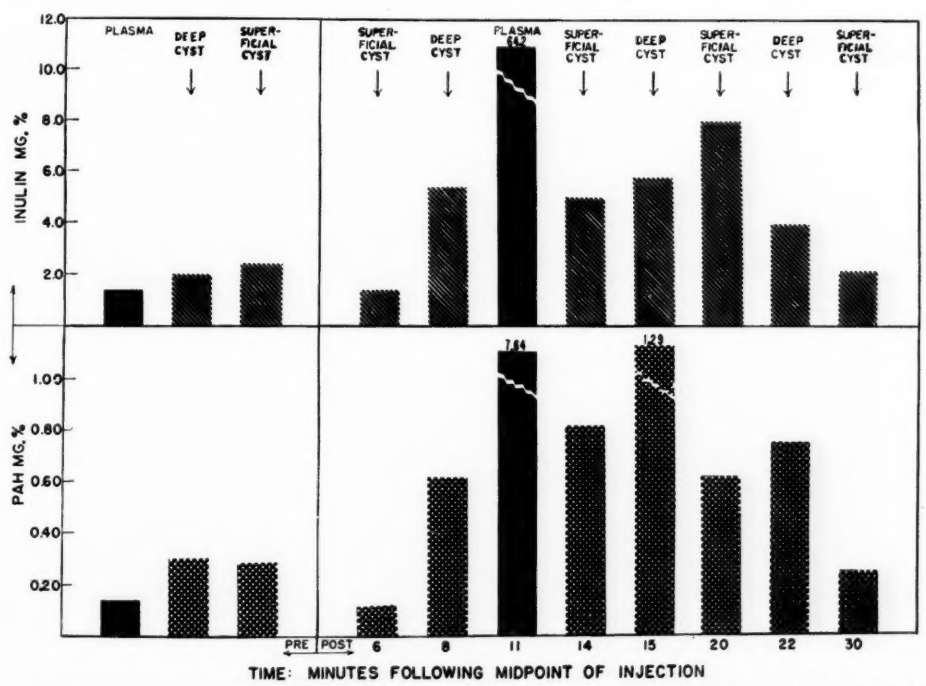

FIG. 7. Relationship of inulin and PAH concentration in cyst fluid before and after single intravenous injection of inulin-PAH solution. Each set of two bars in individual vertical columns represents values from a single CF or plasma sample.

Creatinine Values

Polycystic Kidneys. Values for creatinine concentrations in cyst fluid have been divided into two groups, based on the location of the cysts. These are: (1) those obtained from superficial cysts and (2) those obtained from deep cysts.

FIG. 8. Ratio of creatinine concentrations: cyst fluid/plasma. Case I.

In Figure 8 the ratios of CF to plasma (CF/P) creatinine concentrations are represented for both superficial and deep cysts in Case I. Three of the four superficial samples had CF/P values which approximated 1, whereas values from all of the deep samples exceeded 1, ranging from 2.95 to 4.88. Sixty-seven per cent of all of the superficial cysts sampled to date from polycystic kidneys have shown creatinine concentrations which approximated those in the plasma; whereas all of the deep cysts sampled have had values greater than simultaneous plasma values. Composite creatinine data are recorded in Table IV.

Simple Cysts. Creatinine values in cyst fluid from simple cysts have invariably approximated plasma values, irrespective of the location of the cysts in the kidney. The data from these experiments are included in Table IV.

Electrolyte and Total Solute Concentrations

Polycystic Kidneys. CF and plasma values for Na, Cl, K and total solute concentrations are recorded in Table V. Cyst locations (i.e., superficial or deep) and creatinine values are included for comparison. Plasma electrolyte values have been corrected for plasma water and Donnan factors so as to facilitate comparison with cyst fluid values.* It has been observed that sodium concentrations in polycystic CF fre-

* Plasma values were corrected according to the formula: kP/w = concentration of the electrolyte in the CF; where k = Donnan factor, P = observed plasma concentration, and w = the difference in water content between plasma and CF. k values were as follows: Na = 0.95, K = 0.95; and Cl = 1.02. w was estimated as 0.95, a figure derived from the average difference between plasma protein and CF protein concentrations.

TABLE IV

COMPOSITE CREATININE DATA

	POLYCYSTIC CYSTS										SIMPLE CYSTS							
	Adult								Infant									
	Case I		Case II		Case V		Case VI		Case VII		Case VIII		Case IX		Case X		Case XI	
	mg%	CF/P	mg%	CF/P	mg%	CF/P	mg%	CF/P	mg%	CF/P	mg%	CF/P	mg%	CF/P	mg%	CF/P	mg%	CF/P
Plasma																		
1	1.40		1.50		1.37		1.75		1.37		0.95		0.98		0.92		0.96	
Cyst Fluid																		
1	S 1.16	0.83	D 1.32	8.80	S 1.33	0.97	S 1.30	0.74	S 0.90	0.66	0.90	0.95	0.80	0.82	0.87	0.95	0.82	0.85
2	D 6.83	4.88	? 19.4	12.93	S 1.46	1.07	S 1.46	0.83	S 1.10	0.80	0.80	0.84	0.88	0.90	0.87	0.95	0.95	0.99
3	S 1.16	0.83	? 80.0	53.3	? 34.3	25.0			D 5.30	3.87	0.90	0.95			0.77	0.84		
4	D 4.13	2.95			D 58.5	42.7			S 1.20	0.88	0.90	0.95			0.77	0.84		
5	S 4.23	3.02			D 7.85	5.73			S 1.43	1.04					0.77	0.84		
6	D 5.16	3.69							D 1.87	1.36								
7	S 1.10	0.79							S 1.13	0.82								
8									S 1.00	0.73								

Note: CF/P = cyst fluid/plasma concentration. Plasma values are corrected for an estimated plasma water factor of 0.95. S = superficial cyst; D = deep cyst; ? = indeterminate origin.

Case VII: Values represent serial aspirates from the same cyst fluid.

Case IX: Cysts 1 and 2 represent individual simple cysts.

Case X: Cysts 2–5 represent individual satellite cysts.

Case XI: Cyst 1 right kidney antemortem, cyst 2 left kidney postmortem.

quently exceeded plasma levels although four individual samples (Cases III and V) were less than plasma values. Total solute concentrations, especially in Case I, also exceeded plasma levels. Simultaneous values for sodium and total solutes in individual plasma and CF samples are shown in Figure 9.

Chloride determinations were performed in two cases. In Case I the majority of CF values exceeded plasma values; whereas in Case V only one of four CF values was greater than the plasma concentration. Potassium values, available only in Case I, exceeded the plasma level in all samples.

No consistent relationship was apparent between electrolyte concentrations and either the site of the cyst in the kidney or the creatinine CF/P value.

TABLE V

ELECTROLYTE AND TOTAL SOLUTE CONCENTRATIONS

POLYCYSTIC KIDNEYS

CASE	SAMPLE*		CREATININE □ mg%	NA^+ ●□ mEq/L.	CL^- ●□ mEq/L.	K^+ ●□ mEq/L.	TOTAL SOLUTES mOsm/L.
I	Plasma		1.40	141.4	114.9	4.05	308.0
		S	1.16	154.7	124.2	5.02	358.0
		D	6.83	158.0	129.3	7.03	372.0
		S	1.16	156.5	127.5	4.98	354.0
		D	4.13	149.0	115.4	5.38	
		S	4.23	148.7	118.2	5.20	330.0
		D	5.16	165.7	134.3	4.50	354.0
III	Plasma		2.74	143.5			308.0
		D		14.0			304.0
		D		148.0			306.0
		S		14.1			304.0
V	Plasma		1.37	144.5	116.6		306.0
		S	1.33	158.2	126.6		334.0
		S	1.46	150.0			290.0
		S		144.2			
		S		145.2	117.5		
		S	34.3	104.5	117.5		
		D	58.5	31.0			306.0
		D	7.85	156.7	119.5		322.0
VI	Plasma		1.75	140.0			
		S	1.30	150.0			
		S	1.46	145.7			

* S = superficial cyst fluid; D = deep cyst fluid.

□ Plasma values corrected for plasma water content of 95 per cent.

⊗ Plasma values corrected for the following Donnan factors: Na^+ 0.95; Cl^- 1.02; K^+ 0.95.

Simple Cysts. Plasma and cyst fluid values in five kidneys with simple cysts are recorded in Table VI. CF values for sodium were generally somewhat higher than plasma levels; however, total solute concentrations tended to parallel plasma values. The majority of chloride and

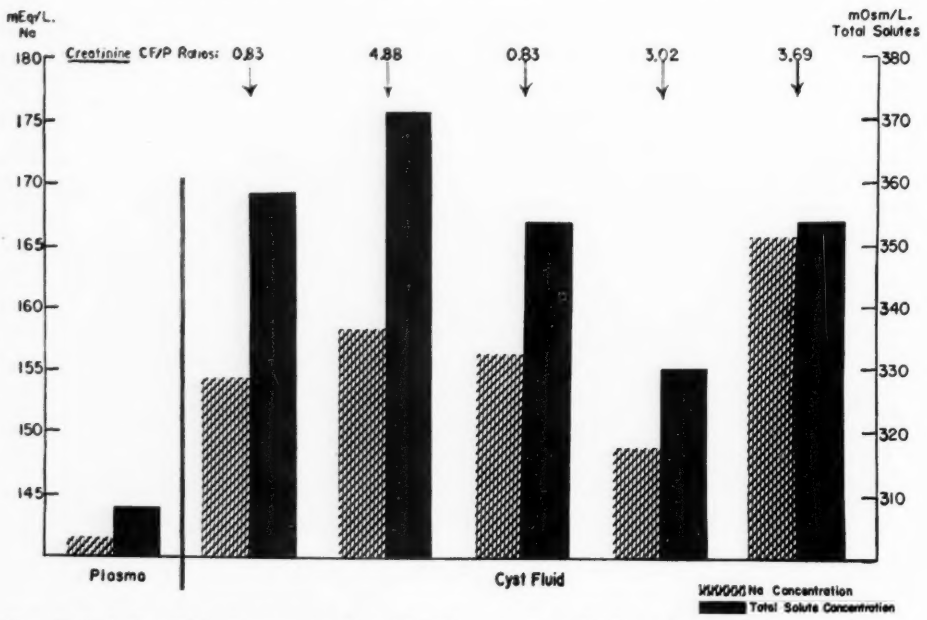

FIG. 9. Relationship of concentrations of sodium and total solutes in cyst fluid and plasma.

TABLE VI

ELECTROLYTE AND TOTAL SOLUTE CONCENTRATION

SIMPLE RENAL CYSTS

CASE	SAMPLE		CREATININE mg%	NA^+ mEq/L	CL^- mEq/L	K^+ mEq/L	TOTAL SOLUTES mOsm/L
VIII	Plasma		0.95	142.7	113.0		
	Simple Cyst		0.90	156.0	114.2	4.8	
IX	Plasma		0.98	138.0		4.45	287.0
	Simple Cysts	1					322.0 *
		2	0.80	146.0		4.21	298.0
		3	0.88	146.5		4.21	298.0
X	Plasma		0.92	141.5	117.5		306.0
	Solitary Cyst		0.87	147.0	118.0		308.0
	Sattelite Cysts	1		147.0			304.0
		2	0.87	148.0	115.6		
		3	0.77	146.5	111.3		300.0
		4	0.77	147.2			296.0
		5	0.77	148.6			
XI	Plasma		0.96	139.5	117.8	4.10	296.0
	Simple Cyst Rt. Kidney		0.82	144.3	118.0	4.13	300.0
	Simple Cyst Left Kidney		0.95 †	136.5 †	110.4 †	6.92 †	300.0 †

Note: Plasma corrections for plasma water content and Donnan factors as in preceding table.

* Bloody sample.

† Postmortem sample.

potassium values in CF did not differ appreciably from plasma values.

Miscellaneous Data

Urine Values. Urine was collected by inlying bladder or ureteral catheters in three studies on adult polycystic kidneys (Cases I, II and IV) and in one case with a simple cyst (Case VIII). By comparison of CF concentrations of creatinine, Na, Cl, K, inulin and PAH with corresponding urinary values, it was possible to establish that none of the CF samples in these four cases represented pelvic urine.

Protein. The concentration of protein was determined in CF samples from one polycystic kidney (Case V) and from the kidney with the solitary cyst plus five surrounding cysts (Case X). In the polycystic study plasma protein was 5.3 gm. per cent and seven CF samples varied from 0.5 to 3.5 gm. per cent. Five of the seven CF values were less than 1.3 gm. per cent. The concentration of protein in CF did not appear to be related to either creatinine CF/P values or electrolyte concentrations. In Case X the plasma protein was 5.7 gm. per cent, CF from the mother cyst 0.8 gm. per cent and CF from the five daughter cysts 0.8, 0.8, 2.6, 0.8 and 2.6 gm. per cent, respectively. The two cysts with the highest protein concentrations could not be differentiated from the remaining cysts on the basis of their creatinine, Na or total solute values.

COMMENTS

In 1947 Lambert reviewed the studies performed in his laboratory on polycystic kidneys.[7] On the basis of careful serial reconstructions of cystic nephrons in adult polycystic kidneys, three groups of cysts, based upon their anatomic locations, were described. These were: (1) glomerular, (2) tubular and (3) excretory cysts. The glomerular cysts were invariably closed units; however, both the tubular and excretory cysts were found to communicate with tubules which were frequently patent and presumably drained into the renal pelvis. In the infant polycystic kidney only closed cysts were encountered. In two moribund patients inulin was injected intraperitoneally prior to death. In both patients cyst fluid samples obtained one hour after death (fifteen and ninety-six hours, respectively, following inulin injection) contained inuloid material. Lambert also presented creatinine and urea values from cyst fluid samples. Although these were not categorized as to the site of the cysts, a gradient of concentrations was noted for both substances. He concluded that cystic nephrons in the adult retain functional activity and play a part in the formation of urine.

Certain of the results obtained in the present study are in essential agreement with the observations of Lambert. Thus the entrance of inulin into cyst fluid of polycystic kidneys noted by Lambert has been confirmed in the present short-term *in vivo* studies. In addition, the existence of a gradient of creatinine concentrations has been confirmed.

It is considered unlikely that fortuitous variation in inuloid blank levels is the explanation for the increase in the postinjection inulin concentrations in the present study. It has therefore been concluded that the inulin injected intravenously entered the cyst fluid of many of the cysts of the adult polycystic kidneys in a relatively short time. This concept is supported by the studies in Case IV wherein a definite increase in CF inulin concentrations was observed by obtaining samples from two cysts both before and after inulin infusion. At least two explanations may be entertained for these observations. The first is that plasma inulin passed with glomerular filtrate into nephrons connecting functionally with cysts; this would imply a continuity of glomerulus and cyst, or of glomerulus, tubule and cyst. The second possibility is that inulin diffused into cyst fluid from the plasma traversing the capillaries in the cyst walls. It is believed that the studies on the solitary cysts may serve to distinguish between the two mechanisms. Thus the failure of inulin concentrations of simple cysts to rise following inulin injection speaks against appreciable diffusion of inulin into these cysts. Although it is realized that the membrane characteristics of simple cyst walls may differ from those of polycystic cyst walls, it is held, nonetheless, that the lack of diffusion into simple cysts is presumptive evidence against diffusion into polycystic cysts. It has been provisionally concluded, therefore, that glomerular filtrate does enter cyst fluid in adult polycystic kidneys. Moreover, this entrance appears to occur irrespective of the location of the cyst in the renal parenchyma.

The studies with PAH tend to confirm the inulin data although the serial analyses on solitary cyst fluid suggest that some diffusion of the PAH ion into CF may have occurred. It has not been possible to determine with certainty

whether the PAH appearing in cyst fluid of polycystic cysts entered by glomerular filtration alone, or whether some was also secreted by the tubules of cystic nephrons.

In the one infant polycystic kidney studied the majority of cysts sampled did not appear to admit inulin. These results are of interest in view of the anatomic demonstration by Lambert that cysts in newborn polycystic kindeys are closed units. The presence of increased inulin concentrations in three of eleven postinjection samples may indicate that a small proportion of the cysts were associated with patent nephrons.* The fact that this patient was twenty-one months old at the time of study, whereas Lambert's two patients were born dead, suggests that certain of the cystic nephrons in the present case may have been of the adult type.

The observation that creatinine CF/P values approximated unity in the majority of superficial cysts and exceeded unity in all of the deep cysts is of considerable interest. Presumably, the superficial cysts lay anatomically in the region of glomeruli and proximal tubules and the deep cysts were more closely related to the distal portions of nephrons. The high CF/P values in deep cysts may therefore be a reflection of the concentration of the glomerular filtrate by the segments of nephrons which are proximal to the cysts. This interpretation implies that cysts not only receive filtrate from their nephrons but that these nephrons maintain functional ability, at least in regard to the reabsorption of water.

The explanation for the greater concentrations of electrolytes and total solutes in cyst fluid than in plasma is obscure. If cyst fluid samples with creatinine CF/P values of one or less consist predominantly of proximal tubular filtrate, a Na CF/P value greater than 1.0 would necessitate the reabsorption of water out of proportion to sodium. On the basis of current concepts of proximal tubular behavior it is not feasible to invoke this explanation. The possibility that the correction factor for plasma water applied to Na was erroneous would not account for the discrepancies observed in total solute concentrations. Further information is necessary before these data may be adequately interpreted. If, as has been suggested above, the high CF/P values for creatinine occur as a result of the removal of water from the glomerular filtrate, the observation that Na and Cl values in CF with high creatinine CF/P ratios are lower than, similar to, or only moderately higher than plasma values suggests that cystic nephrons may also continue to reabsorb Na and Cl.

The concept that CF obtained from different depths in the kidney may be analogous to urine from various levels of normal nephrons is provocative but probably not justifiable. Several considerations militate against accepting the analogy:

1. In the absence of histologic examination, locating a cyst at a point on a nephron must be based upon a hypothetic (in the human) relationship between creatinine urine/plasma ratio and the level of the nephron. The validity of using CF/P creatinine ratios in this manner rests upon the assumptions, (1) that all of the creatinine in the cyst fluid originates from the glomerular filtrate and (2) that the process of concentrating CF creatinine above the plasma creatinine occurs solely through the removal of creatinine-free water from the glomerular filtrate. At the present stage of knowledge, unqualified acceptance of either of these premises is not warranted.

2. If cyst fluid does consist of urine from the area of nephron just proximal to the cyst site; and if, despite the foregoing objections, the site of the cyst may be accurately located by the creatinine CF/P ratio, the CF must be, at least in part, a stagnant pool in which unknown modifications may have occurred. Furthermore, any acute alterations of nephron function would be masked by the diluting effect of the fluid within the cyst.

3. A final deterrent to accepting an analogy between CF and normal intratubular fluid is that the polycystic kidney is a diseased organ and information derived from its CF could not be used unreservedly to explain mechanisms operative in the normal kidney.

SUMMARY AND CONCLUSIONS

In vivo physiologic experiments have been performed on polycystic kidneys and on kidneys with simple cysts. Following intravenous injection of inulin this substance appeared to enter the majority of the cysts of adult polycystic kidneys and some of the cysts of an infant

* In two of the three postinjection cysts with increased inulin concentrations (i.e., the two deep cysts), alternate explanations may be held: (1) Urine samples were not available, and thus either or both CF samples may have represented pelvic urine; or (2) the high inulin concentrations may have been a result of concentration of inuloid blank. Neither possibility, however, is in accord with the findings in the adult polycystic case.

polycystic kidney. In the simple cysts, inulin concentrations did not increase following inulin injection. PAH studies were in essential agreement with the inulin studies in the polycystic studies but in the simple cysts small amounts of PAH appeared to enter the cyst fluid.

The concentrations of creatinine in superficial cysts of polycystic kidneys usually approximated plasma values, whereas the values in deep cysts uniformly exceeded plasma values. Creatinine concentrations in simple cysts invariably approximated plasma values. Sodium, chloride, potassium and total solute concentrations in polycystic cyst fluid were frequently found to exceed plasma levels, irrespective of the creatinine concentrations. In the simple cysts sodium concentrations exceeded plasma values but total solute values were generally in the same range as plasma levels.

On the basis of the foregoing studies it has been concluded that many of the cysts in adult polycystic kidneys and some of the cysts in the infant polycystic kidney studied are connected dynamically to patent nephrons, but that simple cysts do not appear to have this connection. It is considered tenable that cystic nephrons may contribute to the functional capacity of the polycystic kidney.

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REFERENCES

1. Roe, J. H., Epstein, J. H. and Goldstein, N. P. A photometric method for the determination of inulin in plasma and urine. *J. Biol. Chem.*, 178: 839, 1949.
2. Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B. and Graber, M. The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man. *J. Clin. Investigation*, 24: 388, 1945.
3. Bonsnes, R. W. and Taussky, H. H. The colorimetric determination of creatinine by the Jaffe reaction, *J. Biol. Chem.*, 158: 581, 1945.
4. Van Slyke, D. D. and Hiller, A. Application of Sendroy's iodometric chloride titration to protein-containing fluids. *J. Biol. Chem.*, 167: 107, 1947.
5. Wesson, L. G. Methods in Medical Research, vol. 5. Chicago, 1952. Year Book Publishers.
6. Phillips, R. A., Van Slyke, D. D., Hamilton, P. B., Dole, V. P., Emerson, K. and Archibald, R. M. Measurement of specific gravities of whole blood and plasma by standard copper sulfate solutions. *J. Biol. Chem.*, 183: 305, 1950.
7. Lambert, P. P. Polycystic disease of the kidney. *Arch. Path.*, 44: 34, 1947.

Hemorrhagic and Interstitial Pneumonitis with Nephritis*

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THAT acute necrotizing changes in the pulmonary alveoli may occur in patients suffering from generalized hypersensitivity diseases is recognized. Not generally appreciated, however, is the fact that in certain patients recurrent hemoptysis associated with this pathologic process may represent the dominant clinical feature.

HISTORICAL SUMMARY

In 1941 Cannon, Walsh and Marshall[1] demonstrated in rabbits which had been made hypersensitive to egg albumin that instillation of the same antigenic substance into a lung was followed by an acute reaction in that organ. This was characterized by edema, alveolitis with necrosis and hemorrhage into the pulmonary alveoli and pulmonary lymphatics. By their experiments Cannon and his associates confirmed the work of earlier investigators that acute pulmonary lesions could be demonstrated in animals made actively sensitive to a foreign protein when the same protein was applied directly to the lung. They also demonstrated that by passive sensitization animals would respond in the same manner to intrapulmonary instillation of the original antigenic substance.

In the decade of the 1940's, Rich's group[2–4] demonstrated in hypersensitive animals that essentially the same pulmonary lesions as found by Cannon and associates could develop after intravenous administration of the antigen used to make the animals hypersensitive in the first instance. Moreover, they emphasized that the pulmonary lesions in the animals were indistinguishable from the changes which had previously been described by others[5,6] as occurring in the lungs of patients who had acute rheumatic fever. During the same decade there was occasional mention of pulmonary changes in reports[7–10] on sensitivity of human subjects to sulfonamides. These were described as characterized by exudation of edema fluid and fibrin into the alveolar spaces, hemorrhage and interstitial infiltration. Rich and Gregory[2] in 1943 likened the pulmonary lesions of patients sensitive to sulfonamides to those of rheumatic pneumonitis and concluded that the latter condition represented an anaphylactic response. That pulmonary lesions like those seen in sulfonamide sensitivity or in acute rheumatic fever might be encountered in patients who had periarteritis nodosa was reported by Rich in 1945.[3] In the following year Bradley and MacMahon[11] described the features of a patient who had purpura and periarteritis nodosa. In the lungs there were arterial lesions as well as necrotizing alveolar lesions and hemorrhage. The authors believed that the purpuric manifestations could not directly be correlated with arteritis.

In 1948 interstitial pneumonitis[12] was described in a patient who had acute glomerulonephritis and massive pulmonary hemorrhage. In commenting on the case Mallory stated that he had observed similar pulmonary lesions in patients whose kidneys had been injured by sulfonamides and that he had also seen a like picture in the lungs of occasional patients who had acute glomerulonephritis. He commented further that the pathologic changes in the lungs in his case of acute glomerulonephritis were similar to the lesions of acute rheumatic pneumonitis.

In 1952 Baggenstoss[13] reported that in disseminated lupus erythematosus there had been observed atelectizing pneumonitis and basophilic mucinous edema of the pulmonary alveolar walls and of peribronchial and peri-

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vascular tissues, and he also reported interstitial pneumonitis with alveolar hemorrhages.

Thomas and associates[14,15] observed necrotizing and hemorrhagic pulmonary lesions in rabbits exhibiting the generalized Shwartzman phenomenon in which renal cortical necrosis was the most pronounced feature.

There are comparatively few reports in the literature dealing with the clinical phases of pulmonary changes resulting from apparent hypersensitivity states. Nevertheless, in an occasional patient recurrent hemoptysis may be an expression of a generalized hypersensitivity state and may so dominate the clinical picture as to suggest primary pulmonary disease.

Clinical and pathologic experience with cases in which pulmonary bleeding appeared as a manifestation of hypersensitivity prompted us to place these on record. The clinical features of seven cases, together with descriptions of the essential pathologic findings, will serve to emphasize the fact that in hypersensitivity states pulmonary hemorrhage associated with acute necrotizing pulmonary alveolitis may be a prominent feature. In all cases, evidence of renal disease sooner or later was a prominent feature and the clinical diagnosis of glomerulonephritis was made.

CLINICAL ASPECTS OF CASES

CASE I. A twenty-four year old man first registered at the Mayo Clinic on October 12, 1950, complaining of hemoptysis and weakness. About two months before admission he had first noted a cough and hemoptysis. One week previously he had consulted a physician who found extreme pallor but the results of physical examination were otherwise negative. The erythrocyte count was 2,100,000 per cu. mm. of blood.

On admission to the clinic the patient's weight was 161 pounds (about 73 kg.) and his height was 6 feet 2 inches (about 188 cm.). The blood pressure was 110 mm. of mercury systolic and 70 diastolic, the pulse rate 92 per minute and the temperature 98.6°F. The physical examination revealed no abnormalities.

Laboratory studies gave the following results: Six urinalyses revealed a specific gravity ranging from 1.011 to 1.022; albuminuria, grade 2 to 3; erythruria, grade 3 to 5 (on a basis of 1 to 5); pyuria, grade 1 to 2 (on a basis of 1 to 4). The blood hemoglobin was 6.4 gm. per 100 cc.; the erythrocytes numbered 2,230,000 per cu. mm. and the leukocytes ranged from 5,400 to 10,100 per cu. mm. The differential leukocyte count, the blood platelets, bleeding time, whole-blood coagulation time, Rumpel-Leede sign and results of cryoglobulin tests were normal or negative. Examination of a peripheral blood smear showed marked hypochromasia, anisocytosis, poikilocytosis, polychromasia, scattered monocytes, myeloid immaturity and numerous platelets. Examination of a sternal marrow biopsy revealed active normoblastic erythropoiesis. A prothrombin time, the results of a sulfobromophthalein liver function test and direct and indirect serum bilirubin values were normal. The blood urea was 36 mg. per 100 cc.

A roentgenogram of the thorax was negative. A bronchoscopic examination showed changes suggesting chronic bronchitis. Stained specimens of sputum and bronchial secretions were negative for acid-fast bacilli and malignant cells. Roentgenograms of the esophagus, stomach and intestines were negative. Excretory urography and cystoscopy showed no significant abnormalities.

On October 28th the patient coughed up one-half cupful of bright red blood. A few coarse rales were noted in each lung. The erythrocyte count was 1,610,000 per cu. mm. and the concentration of hemoglobin was 4.0 gm. per 100 cc. of blood. He continued to cough up bright red blood and complained of dyspnea until the next day. Bronchoscopy was again done and a large amount of purulent secretion was aspirated from the left upper, main and lower lobe bronchi. Bilateral bronchograms were normal.

From October 28th to October 31st the patient had a fever of 100° to 101°F. The daily urine output while he was in the hospital ranged from 675 cc. to 1,700 cc. He was given an additional 500 cc. of whole blood and further received 3,000 cc. of blood in the period between October 28th and 30th. At the time of his dismissal from the hospital on November 3rd the erythrocyte count was 3,380,000 per cu. mm. and the hemoglobin was 9.0 gm. per 100 cc. of blood. He was dismissed from the care of the clinic on November 6th feeling somewhat improved.

The patient returned on December 1, 1950, and was hospitalized. He stated that he had felt quite well and had no further hemoptysis until one week prior to admission when he noted weakness and sputum again streaked with blood. Physical examination revealed pallor of

the skin and mucous membranes, a radial pulse rate of 80 per minute and blood pressure of 130 mm. of mercury systolic and 80 diastolic. A systolic murmur was noted over the precordium. Examination of the ocular fundi showed an anemic appearance of the disks with mild blurring at the poles probably due to slight edema associated with the anemia. The retinal vessels appeared normal. The results of the physical examination were otherwise negative.

Laboratory examinations gave the following results: The urinalysis showed a specific gravity of 1.008; albuminuria, grade 3; erythruria, grade 5 (on a basis of 1 to 5) and pyuria, grade 1 (on a basis of 1 to 4). Erythrocytes numbered 2,190,000 and leukocytes 5,100 per cu. mm.; the concentration of hemoglobin was 5.8 gm. per 100 cc. of blood. The coagulation time, bleeding time and blood platelets were normal. The blood urea was 162 mg. per 100 cc. and the urea clearance was 6.3 (1.7 cc. per minute). Roentgenograms revealed an infiltrative lesion in the right lower pulmonary field.

Edema of the lower limbs and over the sacrum gradually developed, followed by nausea, vomiting and hiccups. Until January 6, 1951, the daily urine output ranged from 710 to 1,900 cc. The patient eventually became anuric. There was no fever at this time. On January 22nd the blood urea was 478 mg. per 100 cc. Repeated urinalyses revealed isosthenuria, grade 4 albuminuria and grade 2 to 4 erythruria. During the last phase of his illness, hyponatremia and hyperkalemia were noted. The patient died on January 23, 1951, in a state of uremia.

CASE II. A twenty-five year old married white woman registered at the clinic November 6, 1950.* Her chief complaints were cough, hemoptysis, chills, malaise, arthralgia and gross hematuria. Inquiry regarding past history revealed only that a diagnosis of scarlet fever and "strep throat" had been made when she was in the eighth grade. She had two children living and well. At the time of the second pregnancy albuminuria had been noted.

The patient had been delivered of the second normal full-term infant without complications in March, 1950. Three weeks following delivery bilateral loss of hearing appeared, which in two weeks' time progressed to the point of almost complete deafness. No earache or sore throat was noted although the patient stated that she did seem to have a "head cold." She also stated that treatment for this condition had consisted of administration of penicillin and aureomycin, application of argyrol nose packs and nasal radium therapy. Finally these symptoms improved.

In April, 1950, swelling, pain and redness of both knees had suddenly developed and had lasted about one week; then similar changes occurred in her ankles. This had been followed by migratory pains and stiffness in the wrists, elbows and shoulders which persisted up to the time of admission to the clinic. Two weeks prior to admission a "cold," malaise, generalized muscular aching, tightness over the thorax anteriorly and a cough developed. Three or four days later the patient passed "smoke-colored" urine and the home physician noted erythrocytes and albumin in a specimen of urine. One week prior to our examination the patient began coughing up sputum streaked with blood and hemoptysis continued thereafter.

Physical examination revealed a pale, ill appearing woman who coughed repeatedly, with expectoration of bloody sputum. The blood pressure was 110 mm. of mercury systolic and 80 diastolic. The oral temperature on two occasions was 98.8° and 100°F. Rales were heard at both pulmonary bases and over the right upper anterior surface of the thorax. Minimal edema was present over the dorsa of both feet. The results of the remainder of the examination were negative. The muscles and joints seemed normal.

The patient was severely ill and was immediately admitted to the hospital. Laboratory studies gave the following results: Two urine specimens had specific gravities of 1.015 and 1.018; albuminuria, grade 2 (on a basis of 1 to 4); erythruria, grades 2 and 3 (on a basis of 1 to 5); pyuria, grade 1 (on a basis of 1 to 4). Two values for blood hemoglobin were 6.4 and 8.8 gm. per 100 cc. The erythrocytes numbered 2,990,000 and the leukocytes 5,700 per cu. mm. of blood. Examination of a peripheral blood smear, including a differential leukocyte count, showed no abnormalities. The platelet count was 106,000 per cu. mm. of blood, the bleeding time four and one-half minutes, the coagulation time six minutes and the prothrombin time (Quick) twenty-two seconds (normal seventeen to nineteen seconds). Sternal aspiration pro-

* This case has been reported in detail: EDWARDS, J. E., PARKIN, T. W. and BURCHELL, H. B. Recurrent hemoptysis and necrotizing pulmonary alveolitis in a patient with acute glomerulonephritis and periarteritis nodosa. *Proc. Staff Meet., Mayo Clin.*, 29: 193, 1954.

duced a specimen of bone marrow which on microscopic examination seemed normal. The erythrocyte sedimentation rate was 99 mm. in one hour (Westergren method). The blood urea was 56 mg. per 100 cc. An electrocardiogram showed only sinus tachycardia, the heart rate being 110 beats per minute. Roentgenogram of the thorax showed evidence of a diffuse bilateral pulmonary process.

The patient's course in the hospital was brief, with rapid deterioration. She continued to cough, and hemoptysis was frequent and severe. Supportive therapy consisted of transfusion of whole blood and administration of oxygen. Her temperature rose to 104°F. and she died of respiratory insufficiency on November 10, 1950, three days after admission to the hospital.

CASE III. A sixty year old white woman registered at the clinic on October 22, 1951. Her chief complaint was a clear, watery nasal discharge which had been present since June, 1951. This discharge had become bloody in September, 1951, and at this time nasal obstruction developed as well as mild pain over the nasal and temporal regions. On several occasions there was frank epistaxis. One week prior to admission a cough developed which was productive of a moderate amount of clear sputum occasionally flecked with blood. During the same period the patient experienced mild aching in both costovertebral regions. The past history included that of an allergic reaction to penicillin.

Physical examination revealed an obese woman who did not appear ill. Her weight was 185 pounds (about 84 kg.) and her height was 5 feet 3¼ inches (about 161 cm.). The blood pressure was 135 mm. of mercury systolic and 80 diastolic. Her pulse rate was 96 per minute and body temperature was 98°F. The entire nasal mucosa was covered with adherent bloody crusts. Attempts to remove these caused much bleeding. There was a grade 2 systolic murmur at the apex and at the aortic area which was transmitted into the cervical vessels. A few fine rales were heard in the base of the left lung.

Laboratory tests at the time of admission gave the following results: The blood hemoglobin was 11.6 gm. per 100 cc. (77 per cent), erythrocytes numbered 4,200,000 and leukocytes 7,700 per cu. mm. of blood. Examination of a peripheral blood smear, including a differential leukocyte count, showed no abnormalities. An erythrocyte sedimentation rate (Westergren method) was 78 mm. in one hour. Urinalysis showed a specific gravity of 1.022; albuminuria, grade 1; pus cells 3 per high-power field, and erythruria, grade 3 (on a basis of 1 to 5). Tuberculin and histoplasmin skin reactions were positive, and a coccidioidin skin reaction was negative. A thoracic roentgenogram revealed a soft, circumscribed lesion in the right lung, measuring 1.5 cm. in diameter, located near the seventh rib posteriorly. (Fig. 1*a*.) Roentgenograms of the paranasal sinuses revealed a thickened membrane in the right antrum and cloudiness of the ethmoids. A biopsy of the right nasal mucosa showed inflammatory tissue. Excretory urography gave very little evidence of medium in the five-minute film but in the twenty-minute film both kidneys were well outlined and there was medium in the bladder. The upper part of the urinary tract appeared grossly negative. The results of cystoscopic examination were negative.

On November 2nd the lesion in the right lung was found to have approximately doubled its original size. At this time the patient experienced generalized aching and chilling sensations for two to three days and the sputum had become frankly bloody. A catheterized specimen of urine showed 9 pus cells per high-power field, a few granular casts and grade 4 microhematuria. It was not clear how much of this could be attributed to the cystoscopic examination performed two days earlier. The patient's temperature on November 5th was 99.8°F. A roentgenogram of the thorax on November 6th showed a further increase in the size of the lesion in the right lung and there was an additional lesion in the left mid-lung field. Bronchoscopic examination on November 7th showed diffuse chronic bronchitis. The mucous membrane was redder than normal, and there was a moderate amount of mucoid secretion. Bronchial secretions showed two clumps of atypical cells but five specimens of sputum were negative for malignant cells. A biopsy from the left side of the nasal septum on November 12th showed marked inflammatory changes with moderate numbers of eosinophils. A culture of the nasal tissue was negative for fungi.

On November 12th the output of urine decreased and the patient began to complain of weakness as well as of aching over the left upper surface of the chest anteriorly. For one to two days there was a maculopapular rash on her face. A chest roentgenogram on November 14th showed an increase in the distribution of the

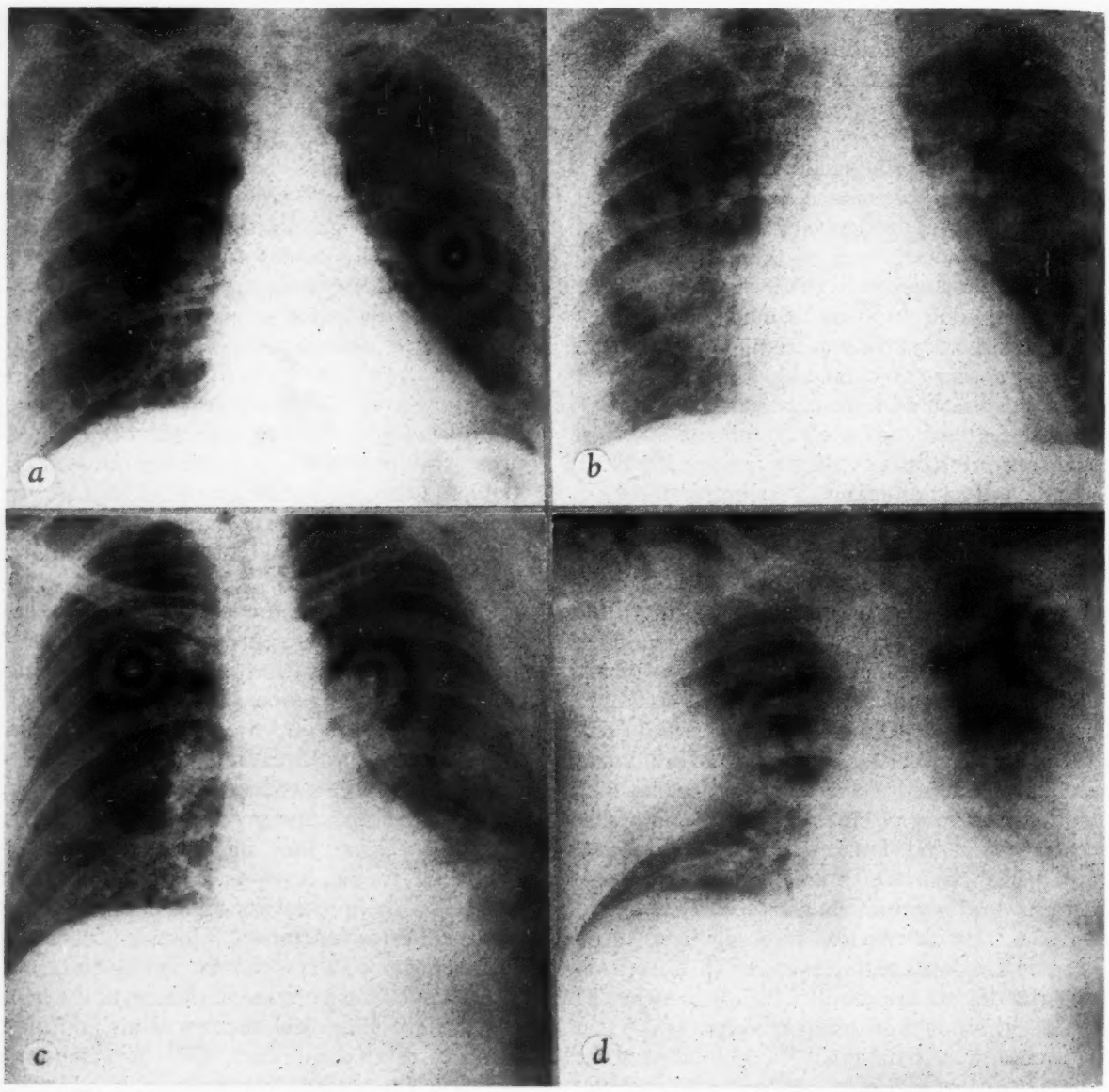

FIG. 1. Thoracic roentgenograms in two of the cases. *a* and *b*, (Case III). Roentgenogram of thorax taken three weeks (October 26, 1951) and three days (November 14, 1951), respectively, before death. Localized lesion in lower portion of right lung was represented in pathologic specimen by organizing alveolar hemorrhage. *c* and *d* (Case IV) Roentgenograms taken five days and one day, respectively, before death.

lesions in both lungs. (Fig. 1*b*.) The cardiac silhouette had increased in size but there was no clinical evidence of cardiac decompensation. An electrocardiogram was normal. The total serum proteins on November 17th were 6.0 gm. per 100 cc. with albumin 3.4 gm. per 100 cc. and globulin 2.6 gm. per 100 cc. The blood urea was 188 mg. per 100 cc. and the creatinine was 10.6 mg. per 100 cc. of blood. The blood pressure was 160 mm. of mercury systolic and 115 diastolic. The temperature was 98.6°F. and the cardiac rate was 115 per minute. There were now many coarse rales throughout both lung fields and the patient was expectorating considerable amounts of dark red blood.

On the evening of November 17, 1951, the patient suddenly became dyspneic while receiving 500 cc. of 5 per cent solution of glucose in water slowly intravenously. Treatment with morphine, digitalis intravenously and oxygen seemed to be followed by some improvement. One hour later a grand mal type of convulsion developed and she died.

CASE IV. A thirty-nine year old white farmer registered at the clinic on July 18, 1950. His chief complaints were hemoptysis and cough of

ten weeks' duration. The past history was not noteworthy. Ten weeks prior to admission he had experienced what he called a "head and chest cold" which lasted three or four days. On the second day, during a paroxysm of coughing, he had noted bright red streaks of blood in his sputum. He stated that he had sought medical attention and had been treated with penicillin. The "cold" had seemed to ameliorate but he had continued having occasional bouts of coughing without hemoptysis. Two weeks prior to admission further head and chest congestion had been noted and he had coughed up considerable bright red blood. Intermittent cough with hemoptysis continued until admission to the clinic. A history of recent dyspnea, marked fatigue and transient aches and pains in his back and extremities was obtained.

The physical examination revealed his weight to be 149 pounds (about 68 kg.) and his height was 5 feet 4½ inches (about 164 cm.). The blood pressure was 122 mm. of mercury systolic and 64 diastolic, pulse rate 60 per minute, temperature 98°F. A few scattered transient rales were noted over the right anterior surface of the chest. The results of examination were otherwise negative.

Laboratory studies gave the following results: Urinalysis revealed a specific gravity of 1.012; albuminuria, grade 2; erythruria, grade 3 (on a basis of 1 to 5); 10 pus cells per high-power field. The blood hemoglobin, erythrocyte and leukocyte counts and differential leukocyte count were normal. A chest roentgenogram showed some exaggeration of the pulmonary markings in both lower lobes. (Fig. 1*c*.)

On July 27th the patient was expectorating large amounts of mucoid sputum containing old blood. On July 28th the blood urea was 102 mg. per 100 cc., the hemoglobin was 8.3 gm. per 100 cc. and the erythrocyte count was 2,960,000 per cu. mm. On July 29th hemoptysis became more profuse and rales were noted over both lung bases posteriorly. On August 2nd the blood urea was 174 mg. per 100 cc. The roentgenogram showed increased evidence of widespread pulmonary involvement. (Fig. 1*d*.) The serum chlorides were 78 mEq./L. and the blood carbon dioxide content was 20.9 mEq./L. The serum sodium was 131 mEq./L. and the serum potassium 3.1 mEq./L. At this time the patient's sputum was bright red and frothy and there were rales in both lungs. He was somnolent and some puffiness of the face and slight pitting edema of the legs were present. The hemoglobin on this date was 6.9 gm. per 100 cc. and the erythrocyte count was 1,960,000 per cu. mm. Hemoptysis continued, oliguria developed and the patient became markedly dyspneic. On August 3, 1950, he died, the immediate cause of death seemingly related to pulmonary insufficiency.

Case v. A nineteen year old white man entered the hospital June 10, 1945. His main complaints were nausea, vomiting and malaise. His past history was negative and he had been well until three weeks prior to admission. At that time he had noted nausea, vomiting, diarrhea and malaise. Two or three days later he had voided rusty colored urine. He had been examined by his home physician who recorded a blood pressure of 126 mm. of mercury systolic and 72 diastolic. The results of physical examination were reported as negative. A specimen of urine contained gross blood. The blood hemoglobin was 56 per 100 cc. The erythrocyte count was 3,560,000 per cu. mm. The blood urea was 148 mg. per 100 cc. Retrograde pyelograms and cystoscopy were not revealing of any disease in the urinary tract. Microscopic examination of urine taken from each kidney revealed many erythrocytes. A diagnosis of acute nephritis had been made.

On admission to the hospital the physical examination revealed a rather pale young man. The heart beat was forceful and a systolic murmur was noted over the base of the heart but there were no other notable findings. The results of an examination of the ocular fundi were negative. The blood pressure was 130 mm. of mercury systolic and 60 diastolic. The temperature was 99°F.

The laboratory studies gave the following results: Three urinalyses revealed a specific gravity ranging from 1.006 to 1.011; albuminuria, grade 2 to 3; erythruria, grade 1 to 3. The blood hemoglobin was 7.4 gm. per 100 cc., erythrocytes numbered 2,290,000 and leukocytes 5,800 per cu. mm. of blood. The results of a routine serologic test for syphilis were negative. Blood urea was 208 mg. per 100 cc., total serum proteins 6.0 gm. per 100 cc. and the serum creatinine was 11.1 mg. per 100 cc. An erythrocyte sedimentation rate was 91 mm. in 1 hour (Westergren method). A portable roentgenogram of the chest was negative.

On June 17th the patient coughed up bright red blood varying in amounts from 10 to 150 cc.

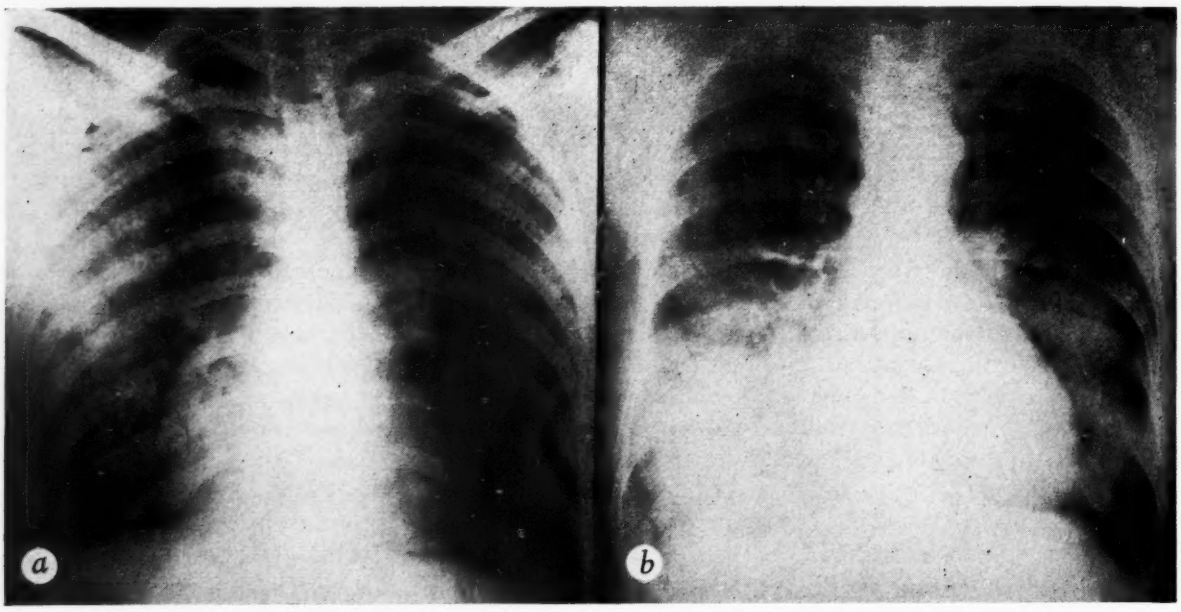

FIG. 2. *a*, (Case v). Roentgenograms of thorax taken one day before death. *b*, For comparison, a roentgenogram of the thorax of a fifty-seven year old woman who had nephritis and recurrent hemoptysis. Roentgenogram taken during a non-fatal attack of respiratory distress. At this time the blood urea level was 126 mg. per 100 cc. of blood. It is suggested that the roentgenographic picture represented hemorrhage resulting from an attack of acute necrotizing alveolitis which later healed. (See Comment for further details of case.)

A few moist rales were noted throughout both lung fields and the temperature was elevated to 102°F. The patient was lethargic and appeared severely ill. A portable roentgenogram of the thorax at this time revealed a diffuse process involving the entire right lung and the upper portion of the left lung. (Fig. 2.) Over the next twenty hours evidence of increasing density of both lungs was noted. The patient died on June 18, 1945, in a state of uremia and with pulmonary insufficiency. During the eight days that he was in the hospital the daily urine output ranged from 1,300 to 2,800 cc. and the highest blood pressure recorded was 132 mm. of mercury systolic and 60 diastolic.

CASE VI. A fifty-seven year old white man entered the hospital on September 9, 1953, under the care of the clinic. The history was obtained from his wife because the patient was acutely ill. He had been apparently well until April, 1953, at which time he began to feel listless. In July he had been struck in the chest with a wrench and soon thereafter had gross hemoptysis which continued for one week. The details regarding the nature and extent of this injury were not available.

Five weeks prior to admission, weakness, pains in the arms and legs, a sore throat and temperature to 100°F. were noted. Treatment at this time consisted of the administration of penicillin and aureomycin. Cortisone was administered for one week; this was discontinued two weeks prior to his examination at the clinic. For one month dark brown or bloody urine had been noted and for ten days before his arrival he experienced nausea, retching and severe headaches.

On physical examination the patient appeared acutely ill and dehydrated. The blood pressure was 210 mm. of mercury systolic and 108 diastolic. The rectal temperature was 100°F. An examination of the ocular fundi showed only minimal narrowing and sclerosis of the retinal arterioles.

Laboratory studies revealed the following data: Urinalysis showed a specific gravity of 1.008; albuminuria, grade 3 (on a basis of 1 to 4); erythruria, grade 5 (on a basis of 1 to 5). The blood hemoglobin content was 10.9 gm. per 100 cc., the erythrocytes numbered 4,000,000 per cu. mm. and the leukocytes 10,800 per cu. mm. A differential leukocyte count showed 7 per cent eosinophils. An erythrocyte sedimentation rate was 36 mm. in one hour (Westergren method). The blood urea was 312 mg. per 100 cc.

During the first two days in the hospital the patient had several convulsions and his condition deteriorated rapidly. Rales were heard in both lungs, the rectal temperature remained about 100°F. and he died in a state of uremia on

September 17, 1953, eight days after his admission to the hospital.

CASE VII. A sixty-two year old white man registered at the clinic and was admitted to the hospital on February 18, 1953.

The family history was noteworthy. The patient's mother had blue scleras and by the age of thirty-five years her hearing was impaired. During her early childhood she apparently had multiple bone fractures and as a young adult had several hemorrhages. Two sisters died of unknown cause at one and one-half years of age, and one of them had blue scleras. One sister was living and well with no apparent abnormalities. The patient had had blue scleras all of his life. By the time of his late "teens" he had had about sixteen bone fractures, often following minor trauma. Since the age of twenty-five years he had had several retinal hemorrhages and at the time of his admission was able to read newsprint only with the aid of a magnifying glass. Impaired hearing was first noted at age thirty years.

In April, 1952, he had a "cold" which was treated with penicillin. In November of the same year cough, sore throat and a "cold" developed. The patient again received penicillin injections. Two or three days later a skin rash appeared, followed by pain, tenderness and swelling in both knees and ankles. The joints seemed warm to touch. These symptoms and signs persisted for two or three weeks. On December 15, 1952, the patient had received another injection of penicillin which was again followed by similar cutaneous and joint involvement together with a temperature to 102°F. On January 1, 1953, he took five cortisone tablets with some improvement in joint symptoms. On February 15th there was a recurrence of the same joint symptoms and signs and he received cortisone for two days. At the time of admission to the clinic his main complaint was soreness and aching in most of his joints.

Physical examination revealed a man who did not appear acutely ill. There was an erythematous area of skin in the center of his forehead and some desquamation of the skin on the anterior surface of the chest, arms and legs. Motions of the spinal column, neck and all peripheral joints were moderately restricted and accompanied by pain. An examination of his eyes showed blue scleras and old bilateral chorioretinitis. The blood pressure was 130 mm. of mercury systolic and 90 diastolic. A grade 2 systolic murmur was heard along the left sternal border in the third interspace.

Laboratory studies gave the following results: Urinalysis showed albuminuria, grade 1 (on a basis of 1 to 4); erythruria and pyuria, grade 1; a specific gravity of 1.012. The hemoglobin content of the blood was 9.6 gm. per 100 cc., the erythrocytes numbered 3,800,000 and the leukocytes 6,500 per cu. mm. of blood. A differential leukocyte count was within the range of normal values. An erythrocyte sedimentation rate (Westergren method) was 127 mm. in one hour. The results of several serologic tests for syphilis were negative.

The day after admission the patient started vomiting. One specimen of vomitus contained about 20 cc. of partially clotted blood.

On February 21st the patient became dyspneic and complained of nausea. No notable changes in blood pressure, temperature or pulse occurred. Bright red, bloody mucus was seen in the pharynx. Rales were heard throughout both pulmonary fields. A portable chest roentgenogram revealed extensive bilateral nodular infiltration of the lungs with multiple calcified nodules in the region of the left hilus. Another blood hemoglobin content was 9.0 gm. per 100 cc. and the erythrocytes numbered 3,440,000 per cu. mm. of blood. The patient died on February 21, 1953.

SUMMARY OF PATHOLOGIC FINDINGS

The pathologic findings in these seven cases will be described in composite fashion. Where special features pertain to a case, due reference to these will be made.

Lesions were found uniformly in the lungs and in the kidneys. In addition, in four of the cases lesions of periarteritis nodosa were noted variously distributed in other organs. In no case was there a blood dyscrasia. Some of the pathologic features are given in Table I.

Lungs. In most of the cases the immediate cause of death was considered to be asphyxia due to pulmonary hemorrhage into the lumina of the tracheobronchial tree. The lungs uniformly showed increase in weight and consolidation of large areas resulting from hemorrhage into the parenchyma. In case VI the combined weight of the lungs was 1,150 gm. while in each of the other six cases the two lungs ranged in weight from 2,130 to 3,260 gm.

Histologic examination of the lungs revealed four processes which were common to each of

the seven cases. These changes were, acute necrotizing alveolitis associated with intra-alveolar hemorrhage, thickening of the connective tissue in the alveolar walls, the presence of prominent and cuboidal cells lining many of the alveolar walls in the areas of hemorrhage and

TABLE I
SYNOPSIS OF PATHOLOGIC FINDINGS

Case	Heart Weight (gm.)	Lung Weight (Combined) (gm.)	Kidney Weight (Combined) (gm.)	Arteritis
I	465	2,445	490	None
II	365	3,260	520	Spleen, liver, gall-bladder, appendix
III	460	2,400	470	Spleen
IV	335	2,680	600	None
V	310	2,980	420	None
VI	485	1,150	405	Spleen, lung, pancreas, kidneys, liver, gall-bladder, appendix, brachial plexus
VII	410	2,130	375	Spleen, pancreas, prostate, rete testis

organization of blood in alveolar spaces. This latter was seen in each of the cases but most extensively in Case III in which this process led to gross foci of pulmonary scarring.

The acute alveolitis was characterized by heavy infiltration into the alveolar walls by cells which in the majority were neutrophilic leukocytes. Eosinophils, though identifiable at times, did not constitute an important element in the cellular infiltrate of the lungs in any of the cases. In involved alveolar walls the cellular infiltration tended to concentrate, producing a nodular thickening of the alveolar wall. (Fig. 3*a* and *b*.) At areas of such concentration of cellular exudate there appeared to be loss of continuity of the alveolar wall, best shown in sections stained for reticulum fibers by the method of Hortega. (Fig. 3*c* and *d*.)

In the areas showing acute necrotizing changes, but not necessarily involving the same alveoli, there were alveolar walls thickened by heavy collagenous bundles. Other alveolar walls were thickened by proliferation of connective tissue which was loose and at times had a swollen mucoid appearance, and contained scattered macrophages, lymphocytes and plasma cells. Occasionally, hemosiderin within phagocytic cells was identifiable in such areas. The thickening of alveolar walls by connective tissue suggested a healed stage of necrotizing alveolitis. Some support for this concept came from those healed lesions which had the same characteristics as to location and size as the lesions of the acute necrotizing process. (Fig. 4.)

Though foci of fibrous thickening of alveolar walls were observed in each case this lesion was observed least commonly in Cases IV and V.

Prominent cuboidal cells lining the alveolar spaces were commonly observed in areas with lesions of the alveolar walls. Rare mitotic figures were present in these cells.

In the alveolar spaces of the involved portions of the lungs the predominant feature was fresh hemorrhage. Strands of fibrin were present in variable number, though never very abundantly. Organization of blood within alveolar spaces, which was present in all cases, was usually seen in comparatively few foci. With the exception of one case (Case III) this process was limited to an occasional alveolar space filled with fibrous tissue containing hemosiderin-laden macrophages or partly obliterated by fibrous tissue and partly by fibrin in process of organization. Intra-alveolar masses of organized blood were frequently covered by cuboid cells similar to those lining the alveolar spaces. In certain areas in Case III the majority of the alveoli contained fibrous tissue representing organized thrombi, relatively large portions of lung being replaced by fibrous tissue. In this case the lesion which was persistently observed in the lower portion of the right lung on roentgenographic examination was composed of conglomerations of organized intra-alveolar blood.

Edema of the lungs was generally absent. In most instances foreign material in the alveolar walls was blood. Peripheral to such areas some of the alveoli contained amorphous acidophilic material characteristic of pulmonary edema. In some such areas there was deposition of hyaline membrane along the alveolar surfaces. Arteritis of the lungs was only an occasional feature in our cases, being found in only one pulmonary artery in only one of the cases (Case VI).

Kidneys. With the exception of Case I the kidneys in the entire series of patients had a similar appearance on pathologic examination and the descriptions that follow pertain to each of the cases except Case I. Grossly the kidneys were enlarged. The combined weights of the kidneys per case varied from about 375 gm. to

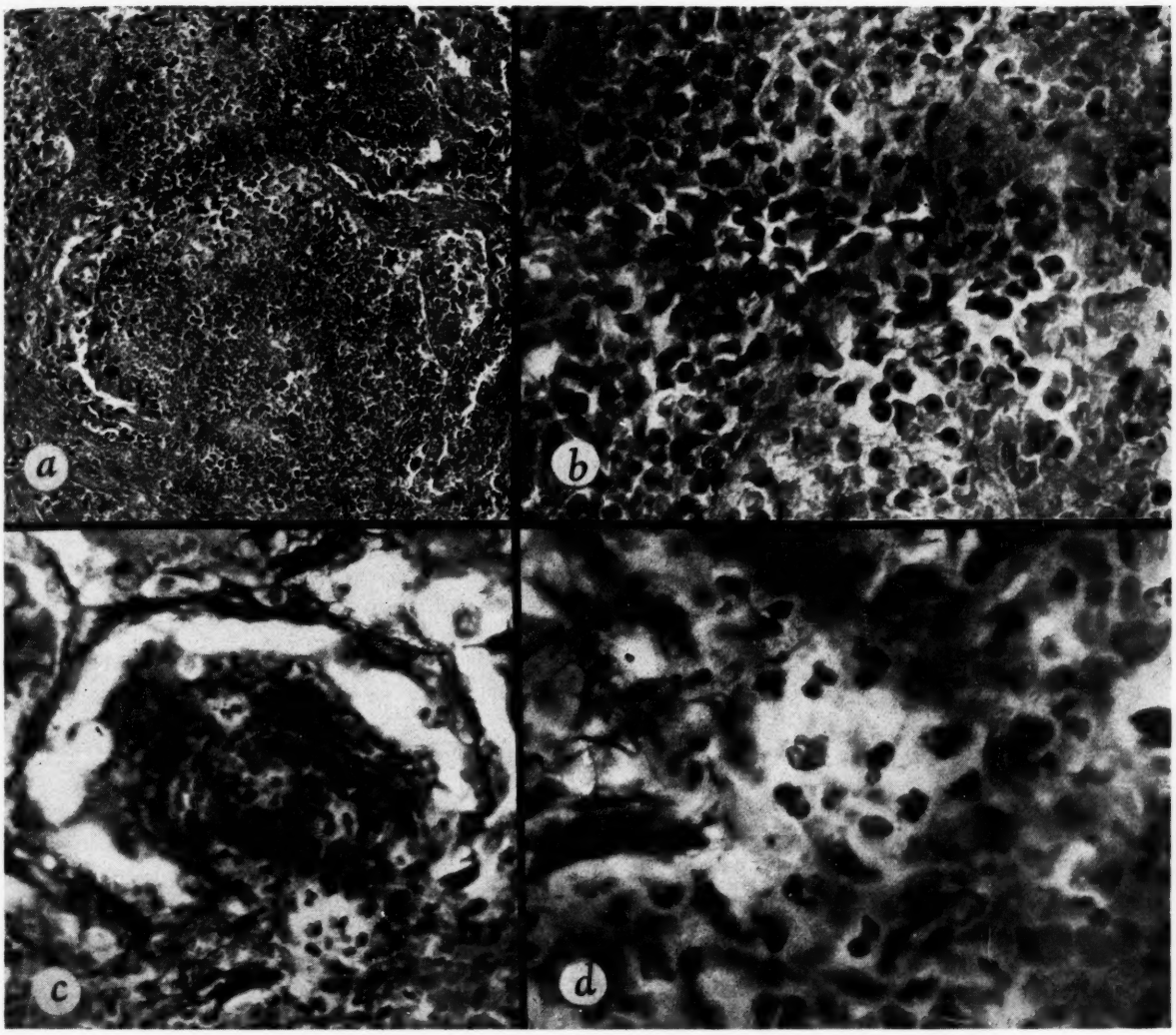

FIG. 3. Photomicrographs of lungs showing acute necrotizing alveolitis with alveolar hemorrhage *a*, (Case VII). Focal necrosis of alveolar wall associated with cellular infiltration. Hemorrhage into alveolar spaces (hematoxylin and eosin, × 145). *b*, (Case VII). Higher magnification of lesion illustrated in *a* shows necrosis of alveolar wall. The cellular infiltrate is made up predominantly of polymorphonuclear neutrophilic leukocytes (hematoxylin and eosin, × 455). *c*, (Case III). Loss of continuity of alveolar wall associated with infiltration by leukocytes. Intra-alveolar hemorrhage (Hortega's reticulum stain, × 350). *d*, (Case III). Higher magnification of lesion illustrated in *c*. At the zone where the reticulum has lost its continuity there is heavy infiltration with leukocytes. Besides these are fragments of reticulum (Hortega's reticulum stain, × 840).

600 gm. The striking feature on gross inspection was a speckled appearance resulting from widespread distribution of hemorrhages.

Histologic examination revealed changes in the glomeruli, tubules and interstitial tissues. While glomerular lesions were common, some glomeruli were uninvolved. About four-fifths of the glomeruli had some lesions which collectively were characterized by necrosis, proliferation of cells of the tufts and of the parietal layer, hemorrhage and exudation of fibrin.

Proliferation of cells of the glomerular tuft gave rise to an enlarged, relatively avascular tuft. Proliferation of the parietal epithelial cells of the glomerulus was common, yielding many glomeruli with well defined crescents. Somewhat variable from case to case was the number of glomeruli in which the processes described had gone on to a later state in which fibrosis of the glomerular tuft was a prominent feature. In some glomeruli so altered, the process was complete, the glomeruli being represented by hyalinized accumulations of collagen. (Fig. 5*a* to *d*.) The relative numbers of hyalinized glomeruli to non-hyalinized ones varied from case to case. In Cases II and IV there were few if any glomeruli

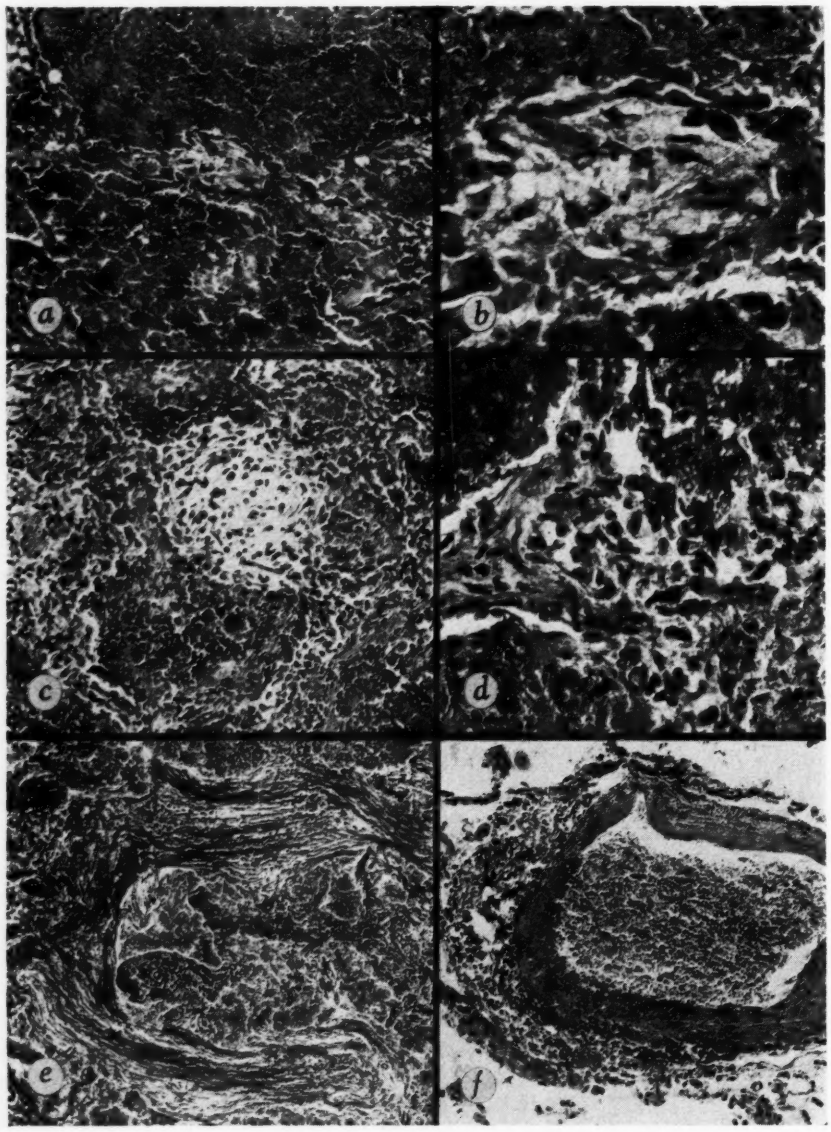

FIG. 4. Photomicrographs of pulmonary tissue. *a*, (Case VII). Low power magnification of alveolar wall showing focal fibrous thickening interpreted as representing a healed acute lesion of hypersensitivity alveolitis. The size and distribution of the scar conform with those features of the acute lesions as illustrated in Figure 3*a* (hematoxylin and eosin, × 145). *b*, (Case VII). Higher magnification of focal fibrous thickening of alveolar wall illustrated in Figure 4*a*. In addition to healed lesions of this type, there were in this case acute necrotizing lesions, as illustrated in Figure 3*a* and *b* (hematoxylin and eosin, × 455). *c*, (Case IV). Focal thickening of alveolar wall by loose connective tissue in which scattered lymphocytes and macrophages are present. The lesion is interpreted as a healed stage of necrotizing hypersensitivity alveolitis. The alveolar hemorrhage is interpreted as resulting from the coexisting acute stages of hypersensitivity alveolitis which were present (hematoxylin and eosin, × 160). *d*, (Case III). Healed and acute hypersensitivity alveolitis. Alveolar thickening of fibrous tissue interpreted as resulting from previous acute stages of hypersensitivity alveolitis. Also present are necrosis and cellular infiltration of alveolar wall associated with intra-alveolar hemorrhage (hematoxylin and eosin, × 400). *e*, (Case III). Extensive scarring of lung from a combination of obliteration of alveolar spaces by fibrous tissue resulting from organization of blood, and also by fibrous thickening of alveolar walls. The latter feature is considered a healed stage of an acute hypersensitivity alveolitis (Verhoeff's elastic tissue stain, × 95). *f*, (Case VI). Pulmonary muscular artery showing segmental necrosis of wall associated with infiltration of leukocytes, mainly neutrophilic (hematoxylin and eosin, ×115).

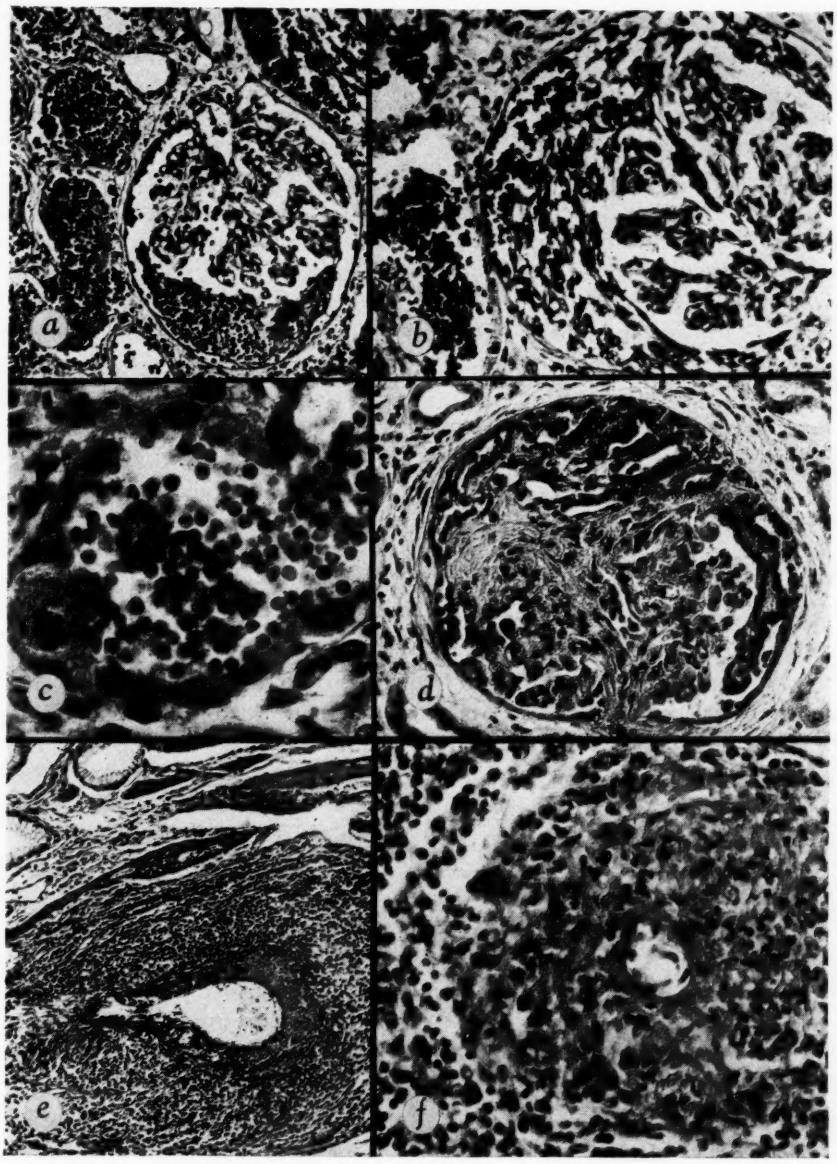

FIG. 5. Photomicrographs of kidneys and arteries. *a*, (Case IV). Hemorrhage into glomerulus and into adjacent proximal convoluted tubules (hematoxylin and eosin, × 165). *b*, (Case IV). Glomerulus associated with proliferation of cells of Bowman's capsule yielding an epithelial crescent (hematoxylin and eosin, × 200). *c*, (Case VII). Proximal convoluted tubule. Hemorrhage into tubule. Regeneration of tubular epithelium as evidenced by mitotic figure (hematoxylin and eosin, × 600). *d*, (Case I). Glomerular changes have progressed to a stage of relative acellularity and fibrosis of tuft. Remnants of adhesions between tuft and parietal layer now indicated by gland-like spaces (hematoxylin and eosin, × 235). *e*, (Case II). Gallbladder. Acute necrotizing arteritis associated with perivascular cellular infiltration (hematoxylin and eosin, × 90). *f*, (Case III). A splenic arteriole showing fibrinoid necrosis of wall associated with cellular infiltration. The infiltrating cells were predominantly neutrophilic leukocytes, but occasional eosinophils were also present (hematoxylin and eosin, × 330).

in which the lesion had progressed to stages of scarring. This is of interest especially in Case IV, in view of the history of ten weeks of pulmonary hemorrhage, and suggests that the abnormal processes in the lungs may have antedated the lesions in the kidneys. Contrariwise, in Case V in which the symptoms were only three weeks in duration there was glomerular scarring in association with glomeruli showing more acute stages of reaction. The scarred

glomeruli suggest that renal disease may have existed for some time before symptoms were noted.

In addition to the glomerular lesions described, there was exudation of fibrin into the glomerular spaces and frank glomerular hemorrhage in other instances. When exudation of fibrin occurred, it was often intimately associated with the loops of the glomerular tufts, and at times the exudation was restricted to only a portion of the tuft. In some instances the position and appearance of the fibrin made it difficult to determine with certainty whether the material was in or outside of the glomerular capillaries. With the hematoxylin and eosin stain the material considered to be fibrin was acidophilic. With the Mallory aniline-blue connective tissue stain it stained red. It gave a reaction for fibrin both with the Weigert fibrin stain and with Mallory's phosphotungstic acid hematoxylin stain. In some instances the presence of similar appearing material within the epithelial crescents suggested fibrinoid necrosis of the crescents.

Hemorrhage within collections of tubules, both in the cortex and in the medulla, was common. In the cortex the tubules containing blood at times showed no recognizable alteration of the epithelium. In other instances there was necrosis of epithelium represented by ghosts of epithelial cells without recognizable nuclei lining the tubules. In still other instances lining cells of the tubules could not be identified and it appeared that the lining of the tubule was now formed by its basement membrane. In certain instances the cortical tubules containing blood were lined by very flat epithelium among which there was an occasional cell with a mitotic figure. The composite appearance of the cortical tubules gave the impression that the process present in the kidneys included cortical tubular necrosis associated with desquamation and regeneration of tubular epithelium. Changes of the type noted in the cortical tubules, other than the presence of blood in the lumen, were not observed in the collecting tubules. It was common to find hemosiderin within the epithelium of the cortical tubules, and in certain areas there were interstitial macrophages containing hemosiderin, suggesting that at some earlier period there had been interstitial hemorrhage.

The most striking interstitial change, however, was represented by foci of cellular infiltration. These varied in size from small foci to widespread areas of involvement. The predominant type of cell was the plasma cell. Eosinophils and lymphocytes were also present but in comparatively insignificant numbers. In Case VI there were necrotizing lesions in renal arteries similar to arterial lesions in other organs in this and other cases.

Separate description of the pathologic features is warranted in Case I as the kidneys appeared to represent a comparatively late phase of the type of nephritis seen and described in Cases II to VII inclusive. In the first case the cortices of the kidneys were yellowish gray and the combined weight of the kidneys was 490 gm. Microscopically, there was extensive involvement of glomeruli characterized by increase in collagen of tufts and adhesions between tufts and parietal layers of the glomeruli. Somewhat more than half of the glomeruli were entirely replaced by collagen. In the majority of the remaining glomeruli there was cellularity of the tufts and parietal layers. These changes associated with adhesions between the two layers of the glomeruli yielded gland-like spaces in the glomeruli. No glomerular necrosis was observed in this case. A small number of tubules contained blood. There was moderate increase of stromal connective tissue. Special stains showed iron pigment in occasional interstitial phagocytes and in the epithelium of a few tubules.

Arteries. In four of the seven cases necrotizing arterial lesions with the microscopic characteristics of periarteritis nodosa were observed. (Fig. 5*e* and *f*.) The vessels involved were small arteries and the lesions predominantly appeared in the form of acute diffuse necrosis of the arterial wall in which the substance of the artery had the uniform eosinophilic appearance of fibrinoid necrosis. Associated with this was cellular infiltration in the wall of the involved arteries, especially in the tissues around the vessels. Neutrophilic leukocytes predominated in the infiltrates but eosinophils, macrophages and lymphocytes were present in smaller numbers.

In Case VII, in addition to acute arterial lesions in sites listed in the table, there was a healed lesion in an artery of the head of the pancreas. In this vessel there was segmental loss of all the layers of the artery, associated with aneurysm formation and thrombosis. In the four cases in which acute arterial lesions were present (Cases II, III, VI and VII) the spleen was involved in each instance, and the gallbladder, appendix, liver and pancreas were each involved twice. In one case there was involvement of the

rete testis and of the prostate. In only one case was an arterial lesion found in the lungs, and in only one case was there arteritis in the kidneys. The aortic valve showed a slight degree of stenosis in Case III.

COMMENT

In the cases here reported the pulmonary alveolitis, with resultant pulmonary hemorrhages, and the nephritis are considered to be manifestations of a hypersensitivity response. The circumstantial evidence strongly favors this view. Of the seven patients four were found on pathologic examination to have periarteritis nodosa, a manifestation of hypersensitivity according to strong evidence.[3,10,16–26]

Acute glomerulonephritis in six of these seven cases also suggests a hypersensitivity state.[18,27–29] In the seventh case (Case I) the nephritis seemed older than in the other six cases but was similar in type. Glomerulonephritis is not uncommon in patients who have periarteritis nodosa.[30–32] This association was present in four of our seven cases.

Additional support for the existence of hypersensitivity phenomena in our cases comes from the fact that in two of the patients (Cases III and VII) there was a history of sensitivity to penicillin. In one other case (Case II) antibiotics including penicillin had been employed prior to an episode of joint pains and malaise, suggesting that this patient also was sensitive to penicillin.

Evidence supporting the view that the pulmonary alveolar lesions observed in our patients represent manifestations of hypersensitivity comes also from experimental work of others. In instances in which pulmonary lesions have been reported in animals made hypersensitive to foreign protein the pulmonary lesions described conformed[1–4] to the changes in the lungs observed in our patients.

Acute cardiac failure, which is believed by some[33] to be an important cause of death among patients dying with acute glomerulonephritis, might be a more convenient than accurate means of explaining extensive pulmonary hemorrhages in patients who have acute nephritis. It is not unlikely that in our patient known not to be uremic at the time of death (Case II) such an explanation for the extensive pulmonary hemorrhage might have been given without careful pathologic study. The presence of necrotizing alveolitis and the predominant exudation of blood rather than plasma into the alveolar spaces are features not adequately explained by acute cardiac failure.

Recurrent hemoptysis occasionally has been observed in patients known to have periarteritis nodosa and is usually explained on the basis of arterial lesions in the lungs. That arterial lesions in the lungs occur among patients who have periarteritis nodosa is an accepted phenomenon, but it is open to question whether these lesions are in themselves responsible for pulmonary bleeding. In our four patients who had lesions of periarteritis nodosa in systemic arteries there was only one patient in whom pulmonary arterial involvement was demonstrated and in this case only one involved artery was seen. In none of the three patients who had nephritis without any lesions of periarteritis were there pulmonary arterial lesions. In our cases, therefore, the acute necrotizing alveolitis seemed a likely source for bleeding into the alveoli of the lungs.

Hemoptysis occurred both in the patients who had periarteritis and in those who had only nephritis. It is recognized that, while the interruption of continuity of alveolar walls could serve as a basis for hemorrhage there could also have been extravasation of blood through less severely damaged capillaries.

While we hold to the thesis that the alveolitis was a manifestation of a hypersensitivity phenomenon, the question whether the alveolitis could be a reaction to uremia merits comment. It is recognized that patients who have uremia may have pulmonary complications.[34] Reference to the clinical abstracts of the cases presented makes it immediately apparent that there is not a consistent relationship between the presence of the alveolitis and the level of blood urea. In five of the six patients in whom blood urea level determinations were made shortly before death the values were elevated and in ranges consistent with those of uremia. However, in the sixth patient (Case II) in whom a terminal blood urea determination was made the value was 56 mg. per 100 cc. of blood. In two of the patients with elevated blood urea levels before death there was little or no nitrogen retention when hemoptysis began (Cases I and IV). In Case I the level two months after the onset of hemoptysis was 36 mg. per 100 cc. of blood. In Case IV the level ten weeks after the onset of hemoptysis was 76 mg. per 100 cc. of blood. The fact that uremia was frequently present at the time of death in the patients reported is

taken as an expression of the coexistence of serious renal lesions in the patients with pulmonary alveolitis rather than indicating that the alveolitis represents a reaction to uremia.

Additional support for this view comes from the fact that, in a study of the lungs of patients who had died in uremia from a variety of conditions unrelated to glomerulonephritis or periarteritis nodosa, necrotizing alveolar changes were not observed. In uremia unrelated to hypersensitivity conditions it is common to find edema, hyaline alveolar membranes, bronchopneumonia, prominent alveolar lining cells and small hemorrhages, but not necrotizing alveolitis.

To test the point whether the alveolitis encountered in our seven cases might have resulted from, rather than caused, alveolar hemorrhage, sections were examined microscopically from patients who had aspirated blood into the lungs from the upper respiratory passages and from patients who had thrombocytopenic purpura. In none of these cases was alveolitis found even in the areas with blood within the alveolar spaces.

Mention should be made of the thickening of alveolar walls by loose connective tissue, at times mucoid, and of the organized blood in the alveolar spaces in each of our cases. The latter process, namely, organization of blood clot within alveolar spaces, was found only in scattered foci in each of six of the cases. In the seventh case (Case III), however, the distribution of organized blood clots was extensive and concentration of this process in certain areas gave rise to gross scarring, which was evident in the gross pathologic specimen.

Among the questions posed by the observations here reported are three: (1) Do the lesions of pulmonary necrotizing alveolitis ever heal by resolution, leaving no recognizable residua? (2) Do some patients have only healed phases of a necrotizing alveolitis at the time of pathologic examination? (3) Are the pulmonary lesions observed in the cases here reported related to other conditions claimed to be allergic manifestations in the lung? Each of these questions may be answered in the affirmative.

A patient who is not one of the seven here reported but whose roentgenogram is reproduced in Figure 2*b* of this paper was a fifty-seven year old woman who had a history of recurrent hemoptysis for a year and a suggestive history of penicillin sensitivity. On her initial visit the thoracic roentgenogram showed extensive involvement by a diffuse process. (Fig. 2*b*.) At this time the blood urea level was 126 mg. per 100 cc. of blood. Subsequently the roentgenographic picture cleared and was interpreted as normal shortly before the patient's death from uremia (blood urea 306 mg. per 100 cc.) two months later.

Pathologically, there was renal disease similar to that in Case I of this report and in relation to a peripheral nerve there was one focus of acute necrotizing arteritis. The lungs showed only extensive collections of intra-alveolar hemosiderin. There were no alveolar lesions, either active or healed, and there was no organized blood in the alveolar spaces.

The conclusion reached in regard to this patient was that her recurrent hemorrhage had been caused by necrotizing alveolitis, as in the patients here reported, but that by the time of death these had healed by resolution. The only remnant of earlier pulmonary hemorrhage was in the form of pigmented alveolar macrophages.

In regard to the second question concerning only evidence of healed alveolitis it is pertinent to mention yet another case which is not part of this report. This involved a thirty-five year old man who gave a history of recurrent hemoptysis starting one and one-half years before his death and after penicillin had been administered for a traumatic epididymitis. Severe hypertension also developed and he died of uremia.

The pathologic examination revealed widespread lesions of periarteritis nodosa from which the arteries of the lungs were spared. Extensive proliferative lesions in the systemic arterioles, of the type seen in severe systemic hypertension, were also found. The lungs showed no acute changes but there were focal alveoli that contained fibrous tissue in which were hemosiderin-laden macrophages. Such lesions were interpreted as representing organized intra-alveolar blood. In addition the alveolar walls showed focal thickening by loose connective tissue similar to that observed in the cases here reported. This would suggest that healed stages of the lesions may be seen in the absence of acute lesions at any given time.

In relation to the third question concerning alveolitis with other types of pulmonary disease, it is recognized that there have been reported focal granulomatous lesions, at times large enough to be recognized clinically, which seem to be manifestations of hypersensitivity. Histologically, these show a loss of pulmonary tissue

and evidences of cellular infiltration, including multinucleated giant cells. Such cases according to Fienberg[35] have been designated variously as periarteritis nodosa, allergic granuloma, giant cell granuloma, granuloma with periarteritis nodosa, eosinophilic granuloma, rhinogenous granuloma, Wegener's granuloma, lupus erythematosus, rheumatic or pararheumatic disorders, Löffler's syndrome and granulomatous glomerulonephritis. In cases of this kind Ehrlich and Romanoff[36] and also Bayley, Lindberg and Baggenstoss[37] have observed thickening of alveolar walls and necrotizing changes similar to those seen in our cases without localized granulomas of the lungs. In the case described by Bayley, Lindberg and Baggenstoss, in which necrotizing pulmonary granulomas were observed, the clinical picture was that of Löffler's syndrome. More recently Fienberg[38] has indicated that the pulmonary condition called "chronic pneumonitis of the cholesterol type" is related to the foregoing type of lesion and seems to result from the effects of hypersensitivity responses in the bronchi.

SUMMARY

In seven patients, believed to have had hypersensitivity states as evidenced by glomerulonephritis in each instance and periarteritis nodosa also in four, hemoptysis was a prominent clinical feature.

Pathologically, the consistent pulmonary lesion was an acute necrotizing alveolitis which bore similarity to pulmonary lesions described previously in hypersensitive animals and humans.

Addendum: Since the preparation of this manuscript Dr. Robert S. Haukohl, of Milwaukee, has shown us the pathologic material pertaining to a male patient fifty years old who had extensive pulmonary hemorrhage as a result of necrotizing alveolitis and in association with acute nephritis of the type observed in our cases.

REFERENCES

1. Cannon, P. R., Walsh, T. E. and Marshall, C. E. Acute local anaphylactic inflammation of the lungs. *Am. J. Path.*, 17: 777, 1941.
2. Rich, A. R. and Gregory, J. E. On the anaphylactic nature of rheumatic pneumonitis. *Bull. Johns Hopkins Hosp.*, 73: 465, 1943.
3. Rich, A. R. The role of hypersensitivity in the pathogenesis of rheumatic fever and periarteritis nodosa. *Proc. Inst. Med. Chicago*, 15: 270, 1945.
4. Gregory, J. E. and Rich, A. R. The experimental production of anaphylactic pulmonary lesions with the basic characteristics of rheumatic pneumonitis. *Bull. Johns Hopkins Hosp.*, 78: 1, 1946.
5. Gouley, B. A. and Eiman, J. The pathology of rheumatic pneumonia. *Am. J. M. Sc.*, 183: 359, 1932.
6. Epstein, E. Z. and Greenspan, E. B. Rheumatic pneumonia. *Arch. Int. Med.*, 68: 1074, 1941.
7. Lederer, M. and Rosenblatt, P. Death during sulfathiazole therapy. *J. A. M. A.*, 119: 8, 1942.
8. Merkel, W. C. and Crawford, R. C. Pathologic lesions produced by sulfathiazole: report of four fatal cases. *J. A. M. A.*, 119: 770, 1942.
9. Pinkerton, H. Pulmonary lesions of sulfonamide. *J. Missouri M. A.*, 40: 364, 1943.
10. French, A. J. Hypersensitivity in the pathogenesis of the histopathologic changes associated with sulfonamide chemotherapy. *Am. J. Path.*, 22: 679, 1946.
11. Bradley, S. and MacMahon, H. E. Clinicopathological conference. *Bull. New England M. Center*, 8: 225, 1946.
12. Case Record of the Massachusetts General Hospital. Case 34342. Presentation of case. *New England J. Med.*, 239: 308, 1948.
13. Baggenstoss, A. H. Visceral lesions in disseminated lupus erythematosus. *Proc. Staff Meet., Mayo Clin.*, 27: 412, 1952.
14. Thomas, L. and Good, R. A. Studies on the generalized Shwartzman reaction. I. General observations concerning the phenomenon. *J. Exper. Med.*, 96: 605, 1952.
15. Thomas, L., Denny, F. W., Jr. and Floyd, J. Studies on the generalized Shwartzman reaction. III. Lesions of the myocardium and coronary arteries accompanying the reaction in rabbits prepared by injection with group A streptococci. *J. Exper. Med.*, 97: 751, 1953.
16. Metz, W. Die geweblichen Reaktionserscheinungen an der Gefässwand bei hyperergischen Zuständen und deren Beziehungen zur Periarteriitis nodosa. *Beitr. z. path. Anat. u. z. allg. Path.*, 88: 17, 1931–1932.
17. Clark, E. and Kaplan, B. I. Endocardial, arterial and other mesenchymal alterations associated with serum disease in man. *Arch. Path.*, 24: 458, 1937.
18. Rich, A. R. The role of hypersensitivity in periarteritis nodosa: as indicated by seven cases developing during serum sickness and sulfonamide therapy. *Bull. Johns Hopkins Hosp.*, 71: 123, 1942.
19. Rich, A. R. and Gregory, J. E. The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity. *Bull. Johns Hopkins Hosp.*, 72: 65, 1943.
20. Wilson, K. S. and Alexander, H. L. The relation of periarteritis nodosa to bronchial asthma and other forms of human hypersensitiveness. *J. Lab. & Clin. Med.*, 30: 195, 1945.
21. Hopps, H. C. and Wissler, R. W. The experimental production of generalized arteritis and periarteritis (periarteritis nodosa). *J. Lab. & Clin. Med.*, 31: 939, 1946.
22. More, R. H., McMillan, G. C. and Duff, G. L. The pathology of sulfonamide allergy in man. *Am. J. Path.*, 22: 703, 1946.

23. GAIRDNER, D. The Schönlein-Henoch syndrome (anaphylactoid purpura). *Quart. J. Med.*, 17: 95, 1948.
24. ALLSOP, J. and SMITH, K. V. A case of the Schönlein-Henoch syndrome. *M. J. Australia*, 2: 418, 1949.
25. PAGEL, W. Polyarteritis nodosa and the "rheumatic" diseases. *J. Clin. Path.*, 4: 137, 1951.
26. ZEEK, P. M. Periarteritis nodosa: a critical review. *Am. J. Clin. Path.*, 22: 777, 1952.
27. LONGCOPE, W. T. The production of experimental nephritis by repeated proteid intoxication. *J. Exper. Med.*, 18: 678, 1913.
28. ALLEN, A. C. The Kidney: Medical and Surgical Diseases, 583 pp. New York, 1951. Grune and Stratton.
29. KAUFMAN, M. A. Focal necrotizing glomerulonephritis and diffuse hypersensitivity angiitis: report of a case with documentation by renal biopsy three years before death. *Arch. Path.*, 57: 80, 1954.
30. KLINGER, H. Grenzformen der Periarteriitis nodosa. *Frankfurt. Ztschr. f. Path.*, 42: 455, 1931.
31. DAVSON, J., BALL, J. and PLATT, R. The kidney in periarteritis nodosa. *Quart. J. Med.* 17: 175, 1948.
32. RALSTON, D. E. and KVALE, W. F. The renal lesions of periarteritis nodosa. *Proc. Staff. Meet., Mayo Clin.*, 24: 18, 1949.
33. WHITEHILL, M. R., LONGCOPE, W. T. and WILLIAMS, R. Occurrence and significance of myocardial failure in acute hemorrhagic nephritis. *Bull. Johns Hopkins Hosp.*, 64: 83, 1939.
34. BURCHELL, H. B. Cardiac manifestations of renal disease including pulmonary edema. *M. Clin. North America*, 35: 1083, 1951.
35. FIENBERG, R. Necrotizing granulomatosis and angiitis of the lungs: with massive splenic necrosis and focal thrombotic granulomatous glomerulonephritis. *Am. J. Clin. Path.*, 23: 413, 1953.
36. EHRLICH, J. C. and ROMANOFF, A. Allergic granuloma of the lung: clinical and anatomic findings in a patient with bronchial asthma and eosinophila. *Arch. Int. Med.*, 87: 259, 1951.
37. BAYLEY, E. C., LINDBERG, D. C. N. and BAGGENSTOSS, A. H. Loeffler's syndrome: report of a case with pathologic examination of the lungs. *Arch. Path.*, 40: 376, 1945.
38. FIENBERG, R. Necrotizing granulomatosis and angiitis of the lungs and its relationship to chronic pneumonitis of the cholesterol type. *Am. J. Path.*, 29: 913, 1953.

Acute Renal Insufficiency Associated with Respiratory Infections*

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ACUTE renal insufficiency has been described secondary to a multitude of agents and diseases; and although the renal pathology involves both the glomeruli and tubules,[1] it is frequently referred to as "lower nephron syndrome." Such a syndrome occasionally accompanies acute infections but appears to be infrequently associated with respiratory infections. We have recently observed several patients who presented histories compatible with an acute onset of uremia and a simultaneous respiratory infection. Three of these patients, in whom studies were made using inulin and sodium para-aminohippurate clearances, and needle biopsies of the kidney, are the subject of this report.

METHODS

Renal function was estimated by the clearance of inulin and sodium para-aminohippurate and the measurement of Tm_{PAH}.[2] The concentration of inulin was determined by the method of Roe et al.,[3] and that of PAH by the method of Smith.[4] Needle biopsy of the kidney was done by the method previously described.[5]

CASE REPORTS

CASE 1. W. T., a fifty-five year old Negro male laborer, was hospitalized because of right lower chest pain. He was stuporous on admission but a subsequent history revealed that the onset of his illness had occurred one week earlier when fever, night sweats, chest pain and a cough productive of a white sputum had developed. He admitted drinking heavily for the three weeks before admission and had consumed ½ gallon of wine on the afternoon of hospitalization.

Physical examination revealed a blood pressure of 150/100, pulse rate of 100 and temperature of 100°F. He was unable to talk coherently. Dullness, decreased breath sounds and crepitant rales were present over the right lung base. The liver was palpable 1 cm. below the right costal margin. There was no costovertebral angle tenderness. The prostate was slightly enlarged.

On examination the urine had a specific gravity of 1.010, 4 plus albumin, 10 to 12 white blood cells with occasional clumps, and innumerable red blood cells per high power field. The hematocrit was 42 per cent, hemoglobin 14 gm. per 100 cc. and white blood count 6,400 with 70 per cent neutrophils. A portable x-ray of the patient's chest revealed a questionable infiltration in the right lower lobe.

On the fourth hospital day the serum sodium concentration was 127 mEq./L., the serum potassium 6.5 mEq./L., the NPN 156 mg./100 cc. and the creatinine 9.9 mg./100 cc. Additional laboratory data, including fluid intake and output, are recorded in Figure 1.

The patient was placed in an oxygen tent and given intravenous fluids and penicillin. He promptly became afebrile during the first forty-eight hours but remained confused. Measured urine volume during the first four hospital days varied between 325 and 700 cc. daily. However, he was incontinent of urine during this time and not all of it was collected. On the fifth hospital day an indwelling catheter was inserted and for the next nine days the urine output varied between 1,000 and 9,000 cc. per twenty-four hours. (Fig. 1.) The NPN reached a height of 272 mg./100 cc. on the tenth hospital day. On the fourteenth day the serum albumin concentration was 2.9 gm./100 cc., and serum globulin 6.2 gm./100 cc.; five days later the serum albumin was 3.6 gm./100 cc., and the serum globulin 3.9 gm./100 cc. On the eight-

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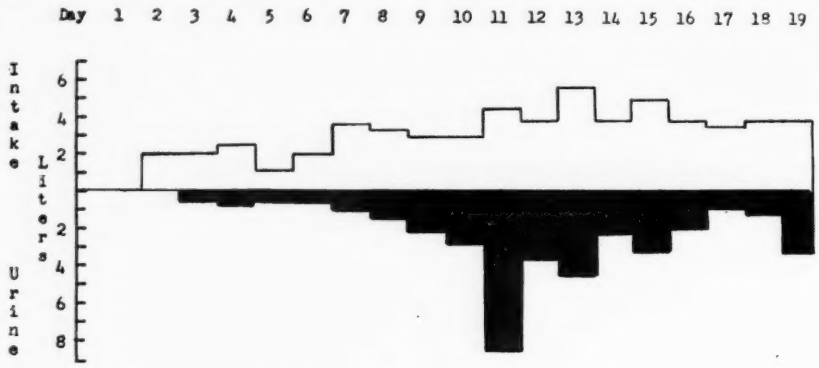
enth day a needle biopsy of the right kidney was performed. Inulin and PAH clearances were determined two days later. (Table I.) One month after the first renal biopsy a second needle biopsy of the kidney was done and the inulin and PAH determinations were repeated. (Table I.)

The initial biopsy (Fig. 2) revealed changes involving primarily the renal tubules. There was tubular dilation and flattening of the epithelium, with protein casts in the lumen. The glomeruli showed moderately increased cellularity and decreased vascularity. These changes were



Day		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	20	22	23	33
NPN	**				156	230		192			272		200		142				36	33
Na	*					127		140					152			157	124	136		139
K	*					6.5		6.0					6.0			4.3	4.6	3.5		5.1
Cl	*					99		103								116			100	109
CO_2	***					17		30								19			34	31
Ca	**					7.7		7.4								8.2			6.5	8.7
P	**					8.3		10.								6.3				4.3
Creat*					9.9															2.0

FIG. 1. Case I. Hospital course: *mEq./L.; **mg./100 cc.; ***mM/L.

The patient gradually improved and by the twentieth hospital day his NPN, Cl^-, Na^+, K^+, HCO_3^-, albumin and globulin had returned to normal. He was discharged after forty-eight days still complaining of some weakness.

TABLE I

Patient	Date	C_{Inulin}* (cc./min.)	C_{PAH}* (cc./min.)	FF* (%)	Tm_{PAH}* (cc./min.)	C_{In}/Tm
W. T.,	1/16	42	254	16	28	1.5
Case I	2/9	71	384	18	93	0.8
	4/20	83	525	16	82	1.0
H. G.,	2/24	58	280	21	38	1.5
Case II	3/12	75	510	15	77	1.0
W. H.,						
Case III	2/20	63	6.7	....	0	...
Normal†	....	127	655	19.3	77	1.6

* Values corrected to 1.73 m^2 S.A. and are the average of three periods.

† Average values for males.[10]

Two months after discharge he was readmitted because of continuing fatigue and weakness. Repeat inulin and PAH clearances and another renal biopsy were obtained. (Table I.)

accompanied functionally (Table I) by a decrease in both inulin clearance and Tm_{PAH}. The C_{In}/Tm_{PAH} suggested approximately equal involvement of glomerular and tubular function.

The second biopsy (Fig. 3) showed improvement in both glomeruli and tubules. The tubular epithelium had become cuboidal, casts were no longer present and there was a decrease in the cellularity of the glomeruli. This was reflected in a return to normal of the Tm_{PAH} and further improvement of the C_{In}. (Table I.) The C_{In}/Tm_{PAH} ratio, however, now showed disproportionate involvement of glomeruli.

The third biopsy (Fig. 4) showed tubules that appeared to be normal but there still appeared to be some increase in cellularity of the glomeruli. Functionally there had been further improvement in the inulin clearance but there was still an abnormal C_{In}/Tm_{PAH} ratio suggesting glomerular damage out of proportion to tubular damage.

CASE II. H. G., a fifty-three year old white male, was admitted to the hospital because of

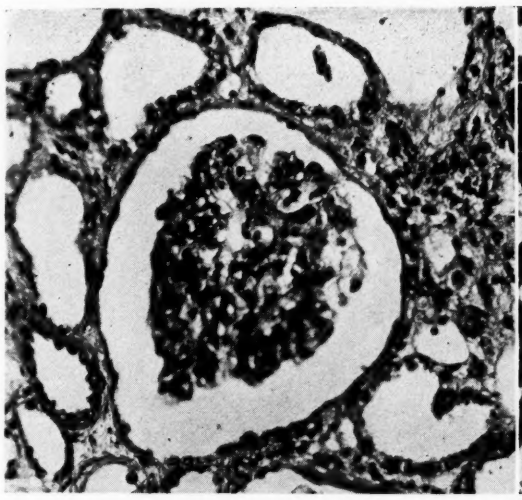


FIG. 2. Case 1. Initial biopsy.

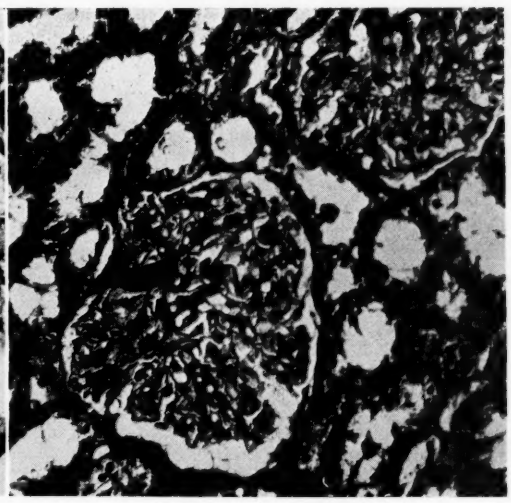


FIG. 3. Case 1. Second biopsy.

shortness of breath. He was discharged from the Army in 1944 for bronchial asthma and since that time he had noted shortness of breath on exertion, associated with ankle swelling for which he had been taking digitalis. Five weeks prior to hospitalization a severe upper respiratory infection developed, with cough, chills and fever and increasing dyspnea. These became progressively more severe up to the time of hospitalization. He admitted consuming 1 pint of wine per day for at least one week prior to admission.

Physical examination revealed a thin, poorly nourished white man who was dyspneic, cyanotic and acutely ill, but whose sensorium was clear. Blood pressure was 120/70, temperature 101.5°F. rectally, pulse 140/min. and respirations 30/min. There was distention of the cervical veins, coating of the tongue and slight injection of the pharynx. Dullness was present at the right base posteriolaterally with coarse, crackling rales; fine rales were heard throughout the remainder of both lung fields. Aside from the tachycardia, the heart was normal. The liver was enlarged 4 cm. below the right costal margin. There was no costovertebral tenderness. On admission, mild pitting edema was present over the sacrum and tibias.

The white cell count was 28,000, with a marked shift to the left, the hematocrit 42 per cent and the Kahn test negative. An alpha streptococcus was cultured from the sputum. On the second hospital day the NPN was 76 mg. per cent, the serum chlorides 77 mEq./L., CO_2 23 mM per L., serum sodium 118 mEq./L. and serum potassium 6.3 mEq./L. Total protein

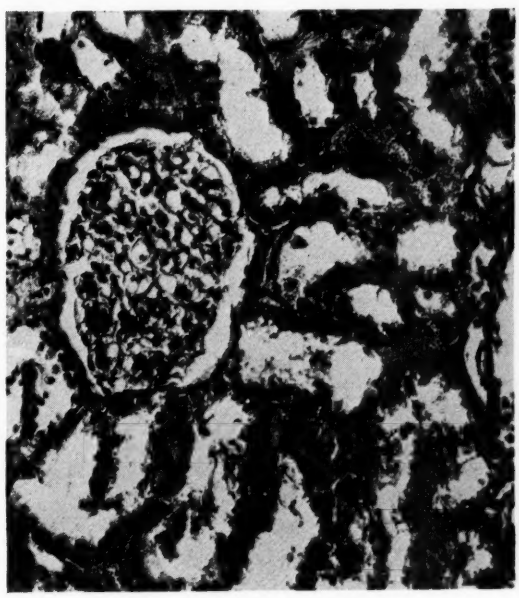
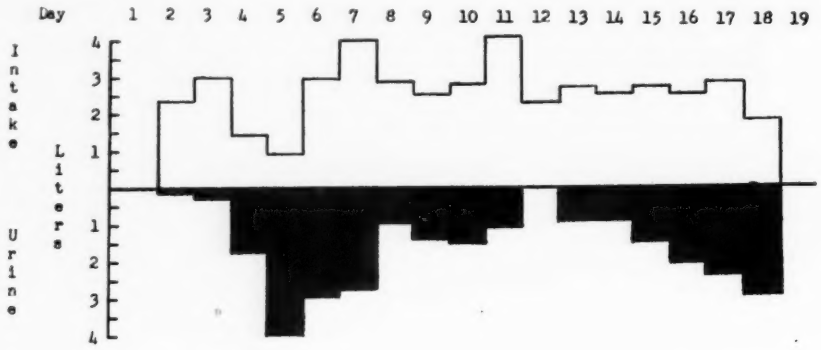


FIG. 4. Case 1. Third biopsy.

was 5.3 gm. per 100 cc., albumin 3.2 and globulin 2.1 gm. per 100 cc. The prothrombin time was normal. Blood cultures on three occasions were negative. The BSP retention, thymol turbidity test, alkaline phosphatase and cephalin flocculation test, determined three weeks after admission, were normal. Urinalysis showed a specific gravity of 1.004 but was otherwise normal. Spinal fluid examination was normal. Portable x-ray of the chest showed the transverse diameter of the heart to be normal. There were stippled densities in both lung fields, especially in the right lower lung field, representing congestive changes with superimposed bronchopneumonia. There was a defi-

nite patch of pneumonitis in the fourth right anterior interspace. Both costophrenic angles were obliterated. Repeat x-rays revealed essentially the same findings, except for clearing of the nodular densities. Skull x-rays and intravenous pyelogram were normal. An electrocardiogram on admission was thought to represent sinus tachycardia and digitalis effect.

Additional laboratory data and urine output are recorded in Figure 5.



Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Na **			118	120	125	129	114	128	146	136	135	139				143			
K **			6.3	4.5	3.9	2.6	1.9	2.6	3.9	4.2	3.5	3.3				5.2			
NPN *	76		82	120	100	104	54	40	42	28				20					
CO_2 ***			23	27	27	20	34	32		20				19					
Cl **			77		71	71	69	85		99				95					
Ca **											7.7		10.8						
Hct	42%	41%								18%		23%	27%	27%	30%	29%			32%

FIG. 5. Case II. Hospital course.

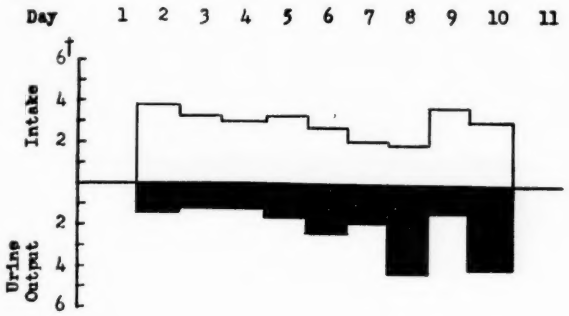
The patient was treated with aminophylline, oxygen, cedilanid,® penicillin, fluids and electrolytes. On the first hospital day it was noted that he was oliguric. On the third hospital day the serum potassium concentration was 6.3 mEq./L. and therapy was started with a cation exchange resin for the adsorption of potassium. His urine output rose to 350 cc./24 hr. and by the fifth hospital day it had risen to 4,000 cc./24 hr. Thereafter his output remained greater than 1,000 cc./24 hr. His hypokaliemia on the seventh day was corrected with oral and intravenous potassium chloride. A needle biopsy of his kidney was attempted unsuccessfully on the sixth hospital day. Inulin and PAH clearances were determined on the tenth hospital day. (Table I.) These showed impairment of both filtration and tubular function. By the tenth hospital day the patient's NPN and serum electrolytes had returned to normal. Transfusions over the next five days improved his anemia, and after eight weeks of hospitalization he was discharged.

Renal function studies initially showed a decrease in both inulin clearance and in Tm_{PAH}, with a C_{In}/Tm_{PAH} ratio which suggested equal involvement of both glomeruli and tubules. After almost a month, at a time when the patient appeared to have recovered clinically, repeat function studies still revealed a decrease in inulin clearance but a normal Tm_{PAH}. This, as well as the C_{In}/Tm_{PAH} at this time, suggested again that glomerular function had lagged behind tubular function in recovery.

Unfortunately, needle biopsies were unsuccessful in this patient on two occasions.

CASE III. W. H., a forty-seven year old Negro male porter, was hospitalized for upper right chest pain. The patient was stuporous at the time of admission but a subsequent history revealed that about five weeks prior to admission he had noted the onset of night sweats and sharp abdominal pain, more marked in the right lower quadrant. This persisted until two weeks before admission, when it shifted to the right upper anterior and lateral chest. The pain was intermittent and not associated with breathing, coughing or movement. He also had an intermittent productive cough of several weeks' duration, and had coughed up blood-streaked

sputum for several days. For the several weeks prior to admission he had been drinking heavily. Ten days prior to admission he was found lying in the hallway of his boarding house and was returned to his room, where he had only an occasional visitor.



Day	1	2	3	4	5	6	7	8	9	10	11
NPN*	224		212	192		240	296	240	272		222
Na **				123		123	129	130	131	137	133
K **				6.5		7.5	6.3	6.3	6.9	4.8	5.0
Cl **						75	77	90			
CO_2***						21	22	23			
Ca *								7.2			

FIG. 6. Case III. Hospital course: *mg./100 cc; **mEq./L.; ***mM/L.: †L./24 hr.

Physical examination showed a well developed, moderately well nourished, semi-stuporous, dehydrated, uncooperative Negro man complaining of intermittent paroxysms of sharp anterior chest pain. There was slight nuchal rigidity. There was fresh, clotted blood in both nostrils. The tongue was swollen, coated and dry. Dullness was present over the right upper anterior chest, and diminished breath sounds were heard over this area and over the right upper chest posteriorly. No rales were heard. The heart was normal except for a grade II harsh, systolic murmur heard loudest over the aortic area. There was marked costovertebral angle tenderness on the right and to a lesser degree on the left. The prostate was slightly enlarged. Deep tendon reflexes were hypoactive bilaterally and there was a generalized decrease in muscle power.

Laboratory studies showed a white cell count of 14,000 with 88 per cent neutrophils, hematocrit 42 per cent. Urinalysis revealed a specific gravity of 1.005, a trace of albumin, no sugar, and 15 to 20 white blood cells per high power field. An NPN was 224 mg./100 cc., and creatinine 13.5 mg./100 cc. The Kahn test was

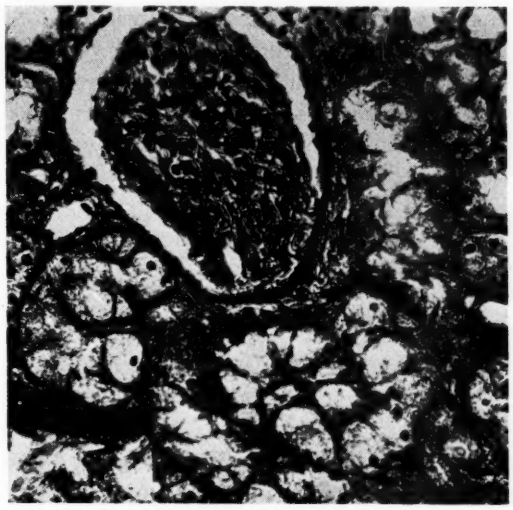


FIG. 7. Case III. Kidney biopsy.

negative. Smear of the sputum revealed gram-positive diplococci predominating, but culture showed a Staphylococcus albus. On the fourth hospital day the serum sodium was 123 mEq./L., the serum potassium was 6.4 mEq./L., and serum chlorides were 75 mEq./L. Culture of the urine revealed Escherichia coli. The BSP retention, cephalin flocculation test, thymol turbidity test and prothrombin time were normal, as was the spinal fluid examination. X-ray of the chest demonstrated right upper lobe pneumonia.

The patient remained semi-stuporous and was treated with penicillin, parenteral fluids and electrolytes. He took very little fluid by mouth. His urine output during the next ten days was never less than 1,000 cc./24 hr., and on several days was as high as 4,000 cc./24 hr. (Fig. 6.)

On the eighth hospital day the NPN reached 296 mg./100 cc., a positive Chvostek sign was demonstrated and the serum calcium was 7.2 mg./100 cc. Convulsive seizures developed and the patient was treated with intravenous calcium gluconate. A right renal needle biopsy was performed on the eighth hospital day. Inulin and PAH clearances were obtained on the ninth hospital day (Table I), and the sodium salt of carboxylic acid resin was started by Levin tube for relief of the hyperkaliemia. The patient's condition remained unchanged although his serum potassium fell to 5.0 mEq./L. On the eleventh hospital day grand mal seizures developed and he suddenly died.

Both the renal biopsy and autopsy showed similar findings. The needle biopsy revealed extensive tubular damage with cell destruction and marked vacuolization. (Fig. 7.) Glomerular

changes were also present, consisting of increased cellularity and decreased vascularity. These findings were thought to be those of acute toxic "nephritis."

Renal function tests done on the following day demonstrated a zero Tm_{PAH} and reduced inulin clearance. These findings suggest primary tubular damage, with a lesser degree of glomerular damage.

COMMENTS

Isolated reports of renal impairment have been made in patients with pulmonary infections. Jeghers[6] reported one case in his series of extrarenal azotemia. This patient showed hydropic changes in the renal tubules at autopsy. Bell[7] included in his series of patients with azotemia ten with pneumonia, four of whom showed hydropic changes in the tubules at autopsy. He also reported one patient with azotemia and delirium tremens who showed no renal abnormalities at postmortem examination.

Renal function studies in pneumonia have shown normal or increased function as far as urea clearance is concerned,[8] although some authors have found impaired renal function.

Several facts appear to be related in the present group of cases. All the patients had been ill for a period of two to five weeks prior to hospitalization. The onset of illness began with symptoms of a respiratory infection. All of the patients were alcoholic and consumed fair amounts of alcohol during their illness before hospitalization. All three were dehydrated and were mentally confused on admission and possibly for several days prior to hospitalization. They were all uremic, with an elevated serum NPN, low serum sodium, bicarbonate, chloride, calcium, and high serum potassium and phosphate. Pulmonary signs were present, suggestive of pneumonia. Subsequent studies showed that one had lobar pneumonia while the remaining two had bronchopneumonia. Biopsy specimens of the kidneys revealed toxic changes in the tubules and were compatible with toxic "nephritis." Repeat biopsy in one of those who recovered showed regression of the pathologic changes. In one patient the findings at autopsy confirmed those of the renal biopsy. The urine specific gravities were low (1.010) and renal function studies with inulin and PAH demonstrated depression of all functions.

Considering the findings in all three patients, the initial renal insult affected the tubules most severely (Case III) and to a lesser degree the glomeruli. Recovery of the tubules occurred rapidly (Cases I and II) so that by the end of four to six weeks tubular function was normal (as measured by Tm_{PAH}) and tubular histology was practically normal. Glomerular function and histology recovered more slowly, and at the end of three months both were still abnormal.

It would appear that in these three patients the peculiar circumstances of alcoholism and acute pulmonary infection led to dehydration and toxic "nephritis" with acute renal insufficiency.

SUMMARY

Three cases in which there was uremia due to acute renal insufficiency associated with acute pulmonary infections are presented.

Renal biopsies showed marked tubular damage which was confirmed by function studies; this appeared to be reversible. Glomerular damage was also demonstrated; this improved but did not entirely disappear.

The etiology of the renal changes is obscure but would appear to be related to a combination of alcoholism, pulmonary infection and dehydration.

REFERENCES

1. French, A. J. Glomerulosclerosis. *Arch. Path.*, 49: 43, 1950.
2. Goldring, W. and Chasis, H. Hypertension and Hypertensive Disease. New York, 1944. The Commonwealth Fund.
3. Roe, J. H., Epstein, J. H. and Goldstein, N. P. A photometric method for the determination of inulin in plasma and urine. *J. Biol. Chem.*, 178: 839, 1949.
4. Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B. and Graber, M. The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dogs and man. *J. Clin. Investigation*, 24: 388, 1945.
5. Parrish, A. E. and Howe, J. S. Needle biopsy as an aid in diagnosis of renal disease. *J. Lab. & Clin. Med.*, 42: 152, 1953.
6. Jeghers, H. and Bakst, H. J. The syndrome of extrarenal azotemia. *Ann. Int. Med.*, 11: 1861, 1937–1938.
7. Bell, E. T. and Kuntston, R. C. Extrarenal azotemia and tubular disease. *J. A. M. A.*, 134: 441, 1947.
8. Abernathy, T. J. and Farr, L. E. Renal physiology in lobar pneumonia. *J. Clin. Investigation*, 16: 421, 1937.
9. Bookman, A. A study of renal function in patients convalescing from acute fevers. *Arch. Int. Med.*, 20: 112, 1917.
10. Smith, H. W. The Kidney. Oxford University Press. New York, 1951.

Renal Hemodynamic Studies in Adults with Sickle Cell Anemia*

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In a previous publication[1] on renal hemodynamics in children four to eleven years of age with sickle cell anemia we observed significant increases in the glomerular filtration rate (GFR), effective renal plasma flow (ERPF), effective renal blood flow (ERBF) and tubular excretory capacity for para-aminohippurate (Tm(PAH)), with a decrease in the filtration fraction $\left(\frac{GFR \times 100}{ERPF}\right)$. More recently Bruck[2] observed similar changes in patients with Cooley's anemia but not in patients with nutritional anemia. McCrory, Goren and Gornfeld[3] demonstrated impairment of urinary concentrating ability ("pitressin-resistance") in children with sickle cell anemia, and also observed that renal clearances of inulin and para-aminohippurate were normal or above normal. Kunz, Mellin, Cheung and Pratt[4] also reported impairment of urinary concentrating ability in patients between the ages of four and fourteen and a half years with sickle cell anemia.

Pathologic changes in the kidney which are associated with sickle cell anemia have not been adequately studied. However, a review of numerous autopsy reports appearing in the literature and a study of our autopsy material[5] revealed progressive changes in the kidney which suggested that renal function in adults might vary from those observed in children. The principal finding in younger individuals is congestion of the renal blood vessels with sickled erythrocytes. In older individuals there are multiple lesions which include granularity of the surface, an adherent capsule, ischemic and hemorrhagic infarcts, areas of cortical necrosis, interstitial fibrosis, abnormal calcification, papillary necrosis and submucosal hemorrhages in the pelvis. Frequently the anatomic renal findings closely resemble those of chronic glomerular nephritis. Arteriosclerotic changes also occur in relatively young individuals and endothelial proliferation is common.

METHODS AND CLINICAL MATERIAL

Patients studied were selected from the Outpatient Department of the John Gaston Hospital, and the diagnosis of sickle cell anemia was established in the Hematology Laboratory. Their ages varied from sixteen to thirty-seven years, and duration of clinical observations in our clinics and hospital varied from two to thirty-six years. All patients had erythrocytes which underwent sickle cell transformation in sealed moist or sodium metabisulfite preparations; all had sickled cells in air-exposed blood smears. Other significant findings included anemia of a regenerative type, leukocytosis, thrombocytosis and hemolytic jaundice. The essential clinical, hematologic and urinary findings are summarized in Table 1. Subjective and objective signs and symptoms associated with recurrent "crises" at one time or another during the years of clinical observations were referable to the skin (ulcers), head, abdomen, and skeletal, cardiorespiratory and central nervous systems. Complaints and findings referable to the urinary tract were infrequent. Hematuria was absent at the time of the clearances in all patients but was observed in one patient, R. W., during a period of hospitalization in 1950. The specific gravity of the urine without water deprivation ranged from 1.006 to 1.018. In 80 per cent of the cases albuminuria was absent or present only in traces; in one case the albuminuria was 1 plus and in another, 4 plus. Blood NPN concentrations

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were obtained in all cases and ranged from 24 to 43 mg. per cent. The blood pressures ranged between 108 to 134 mm. Hg systolic and 60 to 78 mm. Hg diastolic. Although multiple transfusions had been given to these patients, with the exception of A. B., none had received blood within eight months of the time of performance of the renal clearances. All clearances were performed at a time when the patients were not in "crisis."

The patients were given a breakfast of toast and milk at the usual time and 500 cc. of water orally thirty to sixty minutes before the studies were begun. An indwelling catheter was inserted into the bladder and a blank urine specimen was collected. The bladder was irrigated with sterile isotonic sodium chloride solution, and complete emptying was assured by manual expression after the instillation of air. A priming dose of mannitol and para-aminohippurate was given intravenously and followed by a continuous intravenous infusion of these substances in the arm opposite from which blood samples were withdrawn. A twenty-minute period was allowed for equilibration, which resulted in adequate and consistent blood levels. Accurately measured urine collection periods ranged between thirteen and fifteen minutes. Blood samples were withdrawn at the beginning and end of each period. After two periods the concentration of para-aminohippurate (PAH) in the infusion was increased to bring the plasma level of PAH up sufficiently high to measure the maximal tubular excretory capacity for PAH (Tm(PAH)). (Table II.) At this point a thirty-minute period was allowed for equilibration, and the urine and blood samples were collected for two additional periods. The load/Tm(PAH) ratio was found to exceed 1.5 in all cases, indicating saturation of the tubules with PAH.

TABLE I

CLINICAL AND LABORATORY DATA ON ADULT PATIENTS WITH SICKLE CELL ANEMIA

Name	Age (yr.)	No. Years Observed	No. Hospital Admissions	Blood Pressure	Blood Studies							Urinalysis				
					N.P.N. (mg./100 cc.)	Hematocrit (%)	Hemoglobin (gm./100 cc.)	Nucleated RBC per 100 WBC	Reticulocytes (% RBC)	Sickling (%)	Target Cells (%)	WBC	Protein	Specific Gravity (unconcentrated)	Casts	Microscopic Findings
M. L.	16	8	5	124/60	26	23	9.35	7	28.5	12	18	10,800	Neg.	1.012	0	Normal
L. G.	17	10	12	100/50	27	21	6.56	2	19.7	2	10.5	15,100	Neg.	1.015	0	Normal
B. H.	19	17	9	120/60	26	23	6.8	10	29.3	7	11	14,200	Neg.	1.010	0	Normal
S. W.	20	2	3	90/70	24	28	10.1	0	7.0	occ.	2	8,950	Neg.	1.006	0	Normal 2–3 hyaline and granular casts
R. W.	22	3	4	118/50	32	18	6.71	1	21.5	5	4	13,350	Trace	1.015	+	4–8 WBC, 1–3 RBC
A. F.	32	8	14	110/60	31	23	8.3	1	16.0	3	6	8,700	Neg.	1.018	0	Normal
W. P.	33	6	8	108/65	25	32	10.8	0	4.2	occ.	7	6,550	Trace	1.019	0	Normal
M. L. H.	34	8	12	134/78	43	14	6.7	9	22.8	10	4	9,050	1+	1.014	0	Normal
A. L.	37	10	12	110/60	25	23	7.17	1	30.2	1.5	1	12,250	Neg.	1.016	+	5–8 WBC, 10–14 RBC
A. M. B.	37	36	14	118/70	41	15	6.0	3	1.92	10	1.5	21,750	4+	1.006	0	Normal

Mannitol in the blood and urine was determined by the method of Corcoran and Page,[6] and the PAH levels by the method of Smith and co-workers.[7] The plasma levels of mannitol and PAH were plotted on semilog paper. From this graph the levels were determined corresponding to the mid-point of each urine collection period minus two minutes. The body temperature was followed and in no instance was it necessary to make any correction for Tm(PAH).

RESULTS AND COMMENTS

Individual and summarizing data for the patients included in this study are recorded in Table II. The patients have been arranged chronologically according to age. The range and mean values for the GFR, ERPF, ERBF, flow

TABLE II

RENAL FUNCTION IN ADULTS WITH SICKLE CELL ANEMIA

Date	Patient	Age (yr.)	Sex	Surface Area, M_2	Plasma Level at Mid-point Minus 2 Min.		Absolute Clearance Values/Period				Average Clearance Values 1.73 M^2 of Surface Area				GFR × 100/ERPF (filtration fraction)	GFR/Tm(PAH)	ERPF/Tm(PAH)	ERBF/Tm(PAH)	Total Erythrocyte Flow (cc./min.)
					Mannitol (mg./cc.)	PAH (mg./cc.)	GFR (cc./min.)	ERPF (cc./min.)	ERBF (cc./min.)	Tm(PAH) (mg./min.)	GFR (cc./min.)	ERPF (cc./min.)	ERBF (cc./min.)	Tm(PAH) (mg./min.)					
5/15/52	M. L.	16	F	1.365	.280	.0144	92	496	644	.....	116	625	812	79.1	18.6	1.5	7.9	10.3	187
					.268	.0125	99	489	635	.....	....	.....	.....	.....	....	....	....	....	....
					.287	.350	92.5	.....	.....	60.3	....	.....	.....	.....	....	....	....	....	....
					.284	.490	84.5	.....	.....	64.2	....	.....	.....	.....	....	....	....	....	....
1/20/52	L. G.	17	F	1.51	.570	.0152	152	1,050	1,329	.....	148	1,105	1,373	90.9	13.4	1.6	12.2	15.1	293
					.494	.0107	128	870	1,101	.....	....	.....	.....	.....	....	....	....	....	....
					.483	.490	118	.....	.....	77	....	.....	.....	.....	....	....	....	....	....
					.475	.685	116	.....	.....	82	....	.....	.....	.....	....	....	....	....	....
1/13/52	B. H.	19	M	1.43	.468	.0147	130	825	1,071	.....	150	973	1,264	126	15.4	1.2	7.7	10	291
					.442	.0120	122	785	1,019	.....	....	.....	.....	.....	....	....	....	....	....
					.458	.183	116	.....	.....	89.4	....	.....	.....	.....	....	....	....	....	....
					.520	.470	128	.....	.....	120	....	.....	.....	.....	....	....	....	....	....
5/28/52	S. W.	20	F	1.52	.396	.0147	128.5	830	1,203	.....	132	935	1,355	91.8	14	1.4	10.2	14.7	420
					.366	.0132	134	815	1,181	.....	....	.....	.....	.....	....	....	....	....	....
					.468	.300	100.8	.....	.....	79	....	.....	.....	.....	....	....	....	....	....
					.507	.370	100.4	.....	.....	82.6	....	.....	.....	.....	....	....	....	....	....
4/21/53	R. W.	22	M	1.64	.550	.0233	85	780	951	.....	82	831	994	82	10	1.0	9.9	12.1	181
					.506	.0183	91	765	932	.....	....	.....	.....	.....	....	....	....	....	....
					.573	.294	68.3	.....	.....	74.3	....	.....	.....	.....	....	....	....	....	....
					.585	.387	66.5	.....	.....	81.7	....	.....	.....	.....	....	....	....	....	....
5/19/53	A. F.	32	F	1.64	.495	.0223	129	818	1,062	.....	122	825	1,012	91	14.8	1.3	9.1	11.2	187
					.480	.0173	118.5	740	961	.....	....	.....	.....	.....	....	....	....	....	....
					.494	.366	100	.....	.....	84.6	....	.....	.....	.....	....	....	....	....	....
					.460	.478	110	.....	.....	87.3	....	.....	.....	.....	....	....	....	....	....
5/13/53	W. P.	33	M	1.77	.483	.0280	136	665	811	.....	118	606	739	88.3	19.5	1.3	6.9	8.4	133
					.476	.0237	115	585	713	.....	....	.....	.....	.....	....	....	....	....	....
					.448	.307	117	.....	.....	82.2	....	.....	.....	.....	....	....	....	....	....
					.438	.386	119	.....	.....	99.8	....	.....	.....	.....	....	....	....	....	....
2/26/53	M. H.	34	F	1.69	.595	.0334	81.5	605	703	.....	76	589	674	70.5	12.9	1.1	8.4	10.0	114
					.586	.0270	76.5	555	645	.....	....	.....	.....	.....	....	....	....	....	....
					.679	.560	67.5	.....	.....	70.6	....	.....	.....	.....	....	....	....	....	....
					.645	.740	72.0	.....	.....	67.8	....	.....	.....	.....	....	....	....	....	....
5/21/53	A. L.	37	F	1.6	.572	.0363	90	473	614	.....	99	537	696	73	18.0	1.3	7.4	9.5	159
					.570	.0317	110	520	675	.....	....	.....	.....	.....	....	....	....	....	....
					.553	.399	86.3	.....	.....	66.8	....	.....	.....	.....	....	....	....	....	....
					.535	.520	82	.....	.....	68.6	....	.....	.....	.....	....	....	....	....	....
5/28/53	A. B.	37	F	1.66	.475	.0335	65.6	562	661	.....	59	530	643	59.9	11.2	1.0	8.8	10.7	113
					.475	.0236	55.4	490	576	.....	....	.....	.....	.....	....	....	....	....	....
					.514	.525	57.2	.....	.....	55.6	....	.....	.....	.....	....	....	....	....	....
					.507	.696	50.0	.....	.....	59.7	....	.....	.....	.....	....	....	....	....	....

of erythrocyte mass and Tm(PAH) is recorded in Table III. The $\frac{GFR \times 100}{ERPF}$ and also the ratios of GFR, ERPF, and ERBF to the Tm(PAH) have been computed and are included in Tables II and III. The patients in Table III have been grouped as follows: Group A, children with sickle cell anemia, ages four to eleven years previously reported;[1] Group B, adult sickle cell patients, ages sixteen to twenty-two years; Group C, adult patients, ages thirty-two to thirty-seven years; Group D, a combination of all adult patients, ages sixteen to thirty-seven. The normal renal clearance values for adults were obtained from Smith.[8] The normal values for children are taken from previously published data.[9]

TABLE III

COMPARISON OF RENAL HEMODYNAMICS IN SICKLE CELL ANEMIA PATIENTS WITH THOSE OF NORMAL CHILDREN AND ADULTS

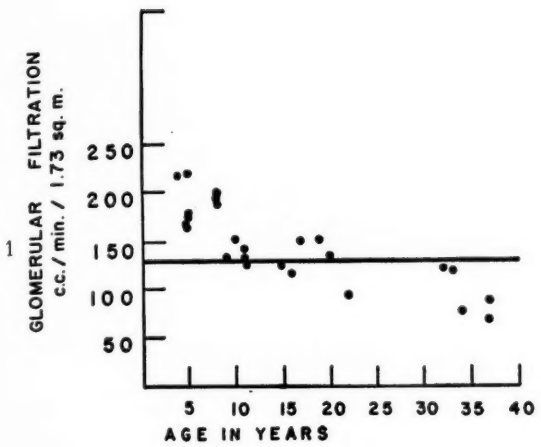
		GFR (cc./min.)	ERPF (cc./min.)	ERBF (cc./min.)	Total Erythrocyte Flow (cc./min.)	Tm(PAH) (mg./min.)	$\frac{GFR \times 100}{ERPF}$	$\frac{GFR}{Tm(PAH)}$	$\frac{ERPF}{Tm(PAH)}$	$\frac{ERBF}{Tm(PAH)}$
Group A:										
Children SCA, 4–11 years (8 pts.–11 clearances)	Range	126–219	722–1,321	1,105–1,833	228–511	88–168	12.7–24.5	1.02–2.2	5.9–10.4	7.9–14.9
	Mean	169	958	1,309	351	120	17.7	1.4	7.9	10.9
Group B:										
Adults SCA, 16–22 years (5 pts.)	Range	82–150	625–1,105	812–1,398	181–420	79.1–126	10–18.6	1.0–1.6	7.7–12.2	10–15.1
	Mean	126	890	1,165	274	93.9	14.3	1.3	9.6	12.4
Group C:										
Adult SCA, 32–37 years (5 pts.)	Range	59–122	530–825	643–1,012	85–187	59.9–91	11.2–19.5	1.0–1.3	6.9–9.1	8.4–11 2
	Mean	94.9	617	753	135	76.5	15	1.25	8.1	10.1
Group D:										
Combined (B & C) Adults SCA, 16–37 years (10 pts.)	Range	59–150	530–1,105	643–1,398	85–420	59.9–126	10–19.5	1.0–1.6	6.9–12.2	8.4–15.1
	Mean	110	753	959	205	85.3	14.6	1.3	8.8	11.2
Normal Adults (9)	Range									
	Mean	127	655	1,200	545	78.9	19.4	1.6	8.3	15.2
Normal Children (8)	Range	110–170	450–750	600–1,119	150–380	65–107	16.0–25.0	1.2–1.7	5.0–8.7	6.7–12.2
	Mean	128	609	893	284	90	21.0	1.4	6.8	9.9

In order to demonstrate graphically the relationship of age of sickle cell anemia patients to renal functions, Figures 1 to 6 were prepared. The solid lines in these figures represent the mean values for normal adults. The total erythrocyte flow was computed by obtaining the difference between the ERBF and the ERPF.

It can be observed from these tables and illustrations that all important renal functions (GFR, ERPF and Tm(PAH)) are eventually impaired as these patients grow older. These functions, however, like those of children, remain at normal or for the most part at supranormal levels until age twenty years is exceeded. The GFR was 82 cc./min./1.73 sq. m. body surface area in R. W., age twenty-two, with the ERPF and Tm(PAH) remaining above the mean for normal adults. In A. F., age thirty-two, the GFR was normal with supranormal ERPF and Tm(PAH). In W. P., age thirty-three, the GFR and ERPF were within the lower limits of normal; the Tm(PAH) being above normal. In the remaining patients, ages thirty-four to thirty-seven, all these functions ranged from approximately 50 to 80 per cent of normal.

The filtration fraction, $\frac{GFR \times 100}{ERPF}$, (Tables II and III and Fig. 6) in these adult patients ranged from 10 in R. W., age twenty-two, to 19.5 in W. P., age thirty-three, with a mean of 14.8. The mean filtration fraction for normal adults is 19.4 and for children with sickle cell anemia, 17.7. Figure 6 reveals that with the exception of four young children this fraction tends to be subnormal. This observation, along with the consistently lower value for the filtration fraction in all groups of adults compared to children with sickle cell anemia (Table III), indicates that glomerular filtration in the older adults decreases out of proportion to the effective renal plasma flow. As previously observed in children,[1] it is apparent that younger adults have a disproportionate increase of ERPF over GFR. In all age groups, therefore, less glomerular filtrate is formed in relation to available plasma than in normal individuals.

The tubular excretory capacity for PAH (Tm PAH) in adults as in the children remains at a



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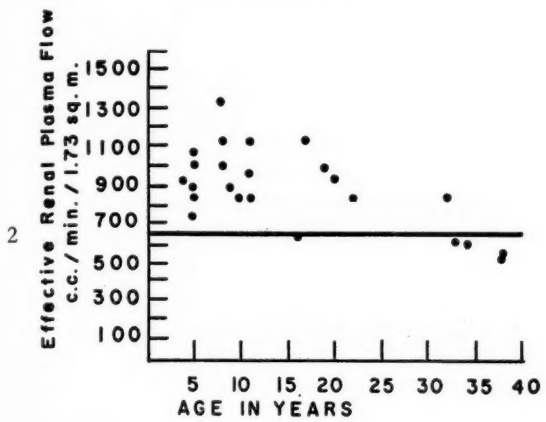

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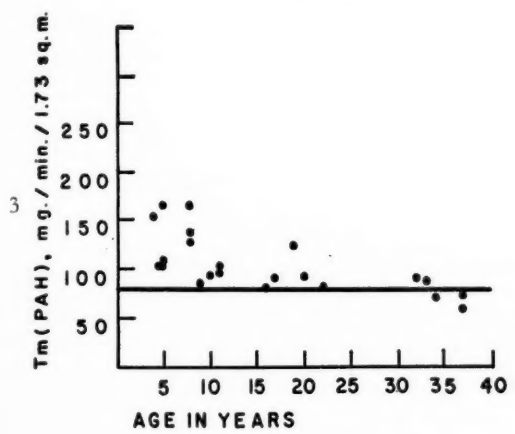

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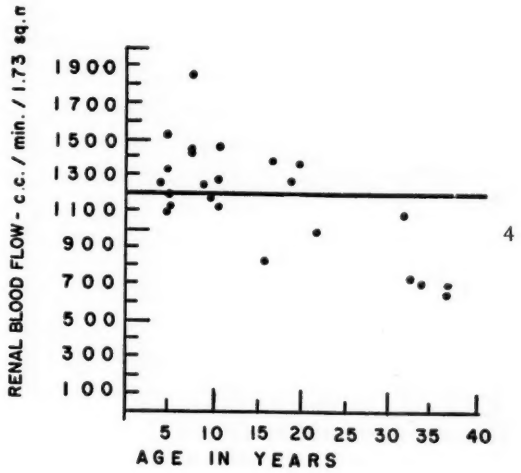
FIG. 1. Glomerular filtration rate in patients with sickle cell anemia. • = average values individual patients; — = mean adult value. All values corrected to 1.73 sq. m. surface area.

FIG. 2. Effective renal plasma flow in patients with sickle cell anemia; symbols as in Figure 1.

FIG. 3. Maximal tubular excretory capacity for PAH in patients with sickle cell anemia; symbols as in Figure 1.



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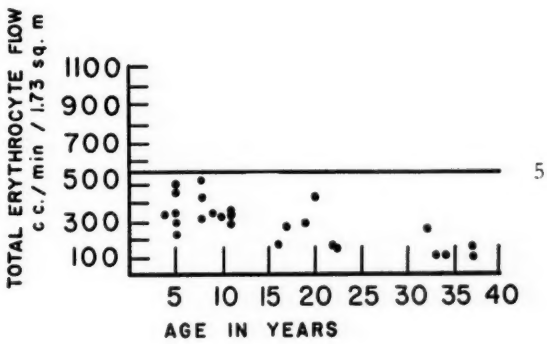

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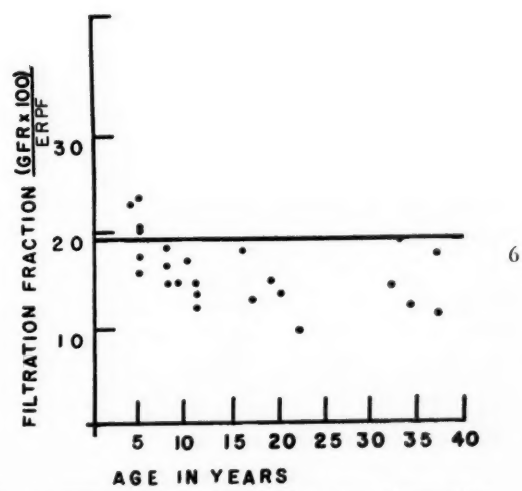

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FIG. 4. Effective renal blood flow in patients with sickle cell anemia; symbols as in Figure 1.

FIG. 5. Total erythrocyte flow in patients with sickle cell anemia; symbols as in Figure 1.

FIG. 6. Filtration fraction $\left(\frac{\text{GFR} \times 100}{\text{ERPF}}\right)$ in patients with sickle cell anemia; symbols as in Figure 1.

higher than normal level until the third decade is completed. (Tables II and III and Fig. 3.) This observation, along with a decreased concentrating ability observed by others,[3,4] can be explained by the fact that facultative water reabsorption and urinary concentration is a function of the distal tubule whereas para-aminohippurate excretion apparently occurs in the proximal convoluted tubule.[9] Therefore, it appears that the function of the distal tubule is affected earlier than the proximal tubule. Further studies of tubular function such as glucose Tm, salt loading experiments, hydrogen ion secretion, etc. are, therefore, indicated in patients of all age groups.

The mean ratios GFR/Tm in all adult groups are similar, i.e., 1.3, 1.25 and 1.3. (Table III.) These ratios are subnormal and unlike those found in children. We observed mean ratios of 1.4 in normal children and in those with sickle cell anemia. Therefore, it may be stated that the glomerular filtration rate decreases out of proportion to Tm(PAH).

The trends in ERPF, ERBF and erythrocyte flow in Figures 2, 4 and 5 and in the mean values for these functions in Groups A, B and C (Table II) reveal proportional changes in each of these functions; this would be expected since there is similarity in hematocrits for each age group.

The mean ERPF/Tm(PAH), which is a measure of tubular perfusion of plasma for the younger adults (sixteen to twenty-two years) is 9.6 as compared to a mean for normals of 8.3. (Table III.) However, the mean ERBF/Tm(PAH) for this group is considerably below the mean for normal adults. Both these ratios are below normal in the older adult group (thirty-two to thirty-five years). In children both these ratios were supranormal, which indicates increased vascularity and/or vasodilation. It appears, therefore, that renal circulation is adversely affected (vasoconstriction and/or occlusion) as these patients become older. Furthermore, the progressive change in the ratios of ERPF and ERBF to Tm(PAH) indicates that the progressive pathology of the kidney is closely, if not primarily, associated with alterations in renal circulation.

SUMMARY

Renal hemodynamics have been measured in ten adult patients with sickle cell anemia between the ages of sixteen and thirty-seven.

The GFR, ERPF and Tm(PAH) are supranormal during early adulthood, as in children, but to a lesser extent.

Between twenty and thirty years of age these functions begin to decrease, with early and greater alterations occurring in the GFR. After the third decade all functions are seriously affected.

The GFR/ERPF is decreased but attributed to a disproportionate decrease in GFR in older adults. In children and young adults the decrease in GFR/ERPF is attributable to a disproportionate increase in the ERPF.

The GFR/Tm(PAH) decreased with age which indicates a disproportionate decrease in GFR.

The ERPF/Tm(PAH) and ERBF/Tm(PAH) indicative of tubular perfusion of plasma and blood, respectively, decreased progressively from abnormally high to subnormal values from childhood through adulthood.

REFERENCES

1. Etteldorf, J. N., Tuttle, A. H. and Clayton, G. W. Renal hemodynamics in children with sickle cell anemia. *Am. J. Dis. Child.*, 83: 185, 1952.
2. Bruck, E. Renal function in anemia. *Am. J. Dis. Child.*, 86: 511, 1953.
3. McCrory, W. W., Goren, N. and Gornfeld, D. Demonstration of impairment of urinary concentration ability or "Pitressin resistance" in children with sickle cell anemia. *Am. J. Dis. Child.*, 86: 512, 1953.
4. Kunz, H. W., Mellin, G. W., Cheung, M. W. and Pratt, E. L. Impairment of urinary concentration in sickle cell anemia. *Am. J. Dis. Child.*, 86: 512, 1953.
5. Diggs, L. W. and Gilmer, W. S. Study in progress.
6. Corcoran, A. C. and Page, I. H. Method for the determination of mannitol in plasma and urine. *J. Biol. Chem.*, 170: 165, 1947.
7. Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B. and Graber, M. Renal clearances of substituted hippuric acid derivatives and other aromatic acid in dog and man. *J. Clin. Investigation*, 24: 388, 1945.
8. Etteldorf, J. N., Tuttle, A. H., Clayton, G. W. and Houck, C. R. Influence of magnesium sulfate on renal hemodynamics in normal children. *Am. J. Dis. Child.*, 83: 301, 1952.
9. Smith, H. W. The Kidney—Structure and Function in Health and Disease. New York, 1951. Oxford University Press.

Urinary Amino Acid Excretion in Renal Disease, with Observations on the Fanconi Syndrome*

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NORMALLY 98 per cent of the amino acids filtered by the glomerulus is reabsorbed during passage down the renal tubules so that only a small quantity appears in the urine.[1] Defects in this normal reabsorptive process have recently been demonstrated in the excessive aminoaciduria of the Fanconi syndrome[2–4] and hepatolenticular degeneration (Wilson's disease).[5,6] The accompanying glycosuria, hyperphosphaturia and abnormal bicarbonate loss in the Fanconi syndrome[2–4] and the occasional appearance of glycosuria in Wilson's disease[6] indicate that other tubular reabsorptive mechanisms may be involved.

The pathogenesis of these tubular dysfunctions is obscure. Although structural lesions are not prominent,[2] some renal disease such as chronic pyelonephritis that is difficult to detect and that affects tubular tissue preponderantly might be responsible. Thus "renal tubular acidosis," which resembles Fanconi's syndrome in certain respects,[7–9] is apparently attributable in many instances to pyelonephritis. It seems appropriate therefore to look for the appearance of aminoaciduria in the course of pyelonephritis or glomerulonephritis when tubular damage is excessive and glomerulotubular imbalance has developed.

According to scattered reports[10–15] urinary and plasma amino acid levels appear to be unaltered in acute and chronic glomerulonephritis in the absence of nitrogen retention. Moreover, intravenous or oral loads of glycine or casein hydrolysate are excreted in normal amounts.[13,14,16] In uremia, plasma amino nitrogen may be normal or slightly elevated[13,17–19] in association with a normal or reduced amino acid excretion.[12,15] A more marked and prolonged elevation in plasma amino nitrogen concentration may follow intravenous or oral loading.[13,14,16] In the nephrotic syndrome an unexplained acute or chronic hypoaminoacidemia may occur[20] but urinary amino nitrogen excretion has been reported as normal before and after administration of oral or intravenous glycine and casein hydrolysate.[15,21,22] However, Squire[23] found that aminoaciduria was not uncommon in nephrotic patients and that, since blood amino acid concentrations were normal, diminished tubular reabsorption apparently was responsible.

These observations are few, however, and characterization of the renal functional abnormality by clearance technics has not been attempted. The present study was therefore undertaken for the purpose of determining, by chromatographic technics, the urinary amino acid excretion during fasting and in response to intravenous amino acid infusion in a variety of acute and chronic renal diseases and in other disorders characterized by tubular dysfunction.

METHODS

The twenty-three subjects of this study were selected from the wards and outpatient clinics of the Presbyterian Hospital. Thirteen subjects suffered from well documented renal disease due to chronic pyelonephritis (four), chronic diffuse glomerulonephritis (four), malignant arteriolar nephrosclerosis (one), benign arteriolar nephrosclerosis (one), disseminated lupus erythematosus (one), acute pyelonephritis (one) and acute glomerulonephritis (one). The patient with acute pyelonephritis was also pregnant. Two subjects with renal dysfunction due to other

* From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital, New York, N. Y. Supported by a grant from the New York Heart Association.

† U. S. Public Health Service Postdoctorate Research Fellow (1951–1952).

causes have been included in this group of renal disease patients. In one (M. DeF.) an unidentified renal tubular lesion had resulted in hyperphosphaturia, hypophosphatemia, glycosuria and osteomalacia with associated multiple pseudofractures (Milkman's syndrome). In the other subject (E. R.) severe renal functional impairment had resulted from carbon tetrachloride poisoning. Amino acid excretion studies were performed in patient E. R. shortly after the onset of spontaneous diuresis following fourteen days of anuria. Eight healthy convalescent subjects free of detectable hepatic or renal disease served as controls.

TABLE 1
PARTIAL FREE AMINO ACID COMPOSITION OF 5 PER CENT AMINOSOL *

Amino Acid	Concentration (mg./500 ml.)
Glutamic acid	3,150
Aspartic acid	3,000
Lysine	2,000
Arginine	1,500
Serine	1,100
Valine	1,050
Leucine	1,000
Isoleucine	1,000
Phenylalanine	650
Proline	600
Threonine	600
Cystine	550
Tyrosine	500
Histidine	450
Methionine	350
Tryptophan	200

* A partial acid hydrolysate of fibrin. All amino acids are in the natural levo form except tryptophan, which is a mixture of DL and L forms. Total (bound plus free) amino acid content 25 gm./500 ml. However, only free amino acid concentrations, determined chromatographically, are shown here, with the exception of isoleucine, phenylalanine and tryptophan which were determined either by chemical or microbiologic assay and therefore include both bound and free forms. Additional but unmeasured quantities of glycine and alanine are also present.

The amino acid mixture used in these studies was a partial acid hydrolysate of fibrin (aminosol®*) supplemented with tryptophan and methionine, containing 25 gm. of amino acids in 500 ml. of water. The composition of this mixture as determined chemically and microbiologically by Abbott Laboratories and chromatographically in this laboratory is shown in Table 1. Only free amino acid concentrations are shown in this table, with the exception of isoleucine, phenylalanine and tryptophan for which total ("bound" plus free) amino acid concentrations are presented. No effort was made to determine the relative amounts of free and "bound" amino acids, although from Table 1 and other quantitative studies[24] it appears that roughly two-thirds of the amino acids in aminosol are in the free form.

* Generously supplied by Abbott Laboratories, North Chicago, Ill.

All studies were performed in the resting, fasting state following the ingestion of 500 ml. of water. Urine was collected by voluntary bladder emptying. Following collection of urine for one to three hours, an infusion of 5 per cent aminosol was administered intravenously at a rate sufficient to deliver approximately 500 ml. in two to four hours.* In some subjects hourly urines were collected throughout the time of infusion; in others all urine voided during the period of infusion was pooled. Amino acid excretion reached a maximum during the second or third hour of infusion and corresponded qualitatively to that revealed by the pooled collection. Urine volumes during the fasting and infusion periods were measured and an aliquot of each was preserved under toluene at 0°C. until analyzed one to eight weeks later. No destruction of amino acids occurred during storage for as long as four months.

Urinary amino acids were determined by a modification of the two-dimensional paper chromatographic method of Williams and Kirby[27] and by the more recent small paper technic of Dent[28] employing duraluminum racks on which twelve 20 by 20 cm. chromatograms could be made simultaneously. Ultrafiltrates of urine containing protein were prepared by filtration through collodion sacs under 150 mm. mercury negative pressure;[29] 25 μl. of urine or ultrafiltrate were analyzed in all subjects. Phenol (4 parts phenol, 1 part water) and collidine-lutidine (1 part each, collidine, lutidine and water) were used as solvents[28] and between "runs" all chromatograms were dried overnight in a hood under forced draft. Color

* The average rate of infusion was slightly slower in patients with renal disease (2.5 ml./min.) than in normal subjects (2.9 ml./min.) owing to a mild intolerance to the mixture in a few patients with renal insufficiency. The quantities infused were roughly comparable, however, and slight differences in infusion rates appear to be inconsequential in terms of over-all excretion.[25,26]

was developed with 0.15 per cent ninhydrin in *n*-butanol. The stability of amino acids was routinely confirmed by a chromatogram following acid hydrolysis of the urine,[29] thereby avoiding confusion between pure amino acids and ninhydrin-reacting peptides in unhydrolyzed urines. Whatman No. 4 filter paper was used in preference to Whatman No. 1 for large paper squares because the "solvent runs" were shorter although resolution of faint spots was less satisfactory. Whatman No. 1 filter paper was used for the small paper squares. After Dent's[28] introduction of the small paper technic, the cumbersome and laborious use of large papers was abandoned. The advantages of small papers were many: (1) Twelve chromatograms could be run simultaneously; (2) the time required for solvent runs was reduced from eighteen to twenty-four hours to five to ten hours; (3) the ideal concentration for resolution of pure amino acid standards was one-half to one-tenth that required for large papers; (4) urinary amino acids in low concentration were more readily identified; and (5) manipulation was simplified.

Amino acid standards* were run simultaneously on separate papers as references to assist in the positional identification of unknown urinary amino acids. Identification was further facilitated by the routine heating of all small papers for five minutes at 85° to 90°C. immediately following application of 0.15 per cent ninhydrin. Variations in the color of spots developed in this manner readily distinguished many overlapping and adjacent spots which separated poorly. Twenty-one amino acids could be resolved by this technic. However, leucine could not be easily distinguished from isoleucine nor methionine from leucine (and/or isoleucine). Methionine usually appeared as methionine sulfoxide which, according to Dent,[3] probably results from the oxidation of methionine during storage or in preparation of the chromatogram. More precise analytic methods for the identification of cysteic acid, which was destroyed during the solvent runs, and of methionine were not employed.

No effort was made to measure individual or total amino acid excretion quantitatively. A rough estimation of individual amino acid concentration was made by adopting an arbitrary scale of + to ++++, depending on the size and color strength of the ninhydrin complex. Amino acid spots visible only by transmitted light were characterized as + and large spots of intense color as ++++. The use of data expressed in this way to detect significant deviations from the normal amino acid output appears to be justified by the characteristic chromatographic patterns of normal individuals over a wide range of urine volumes[3,30,31] and by the strikingly abnormal patterns that usually appear in the Fanconi syndrome[3] and Wilson's disease[11,32] when reabsorption of amino acids is defective.

Inulin and p-aminohippurate* clearances[33,34] were determined in several patients with renal disease within a few days prior to or following studies of amino acid excretion. Although intravenous aminosol in the quantities used is unlikely to alter renal function acutely,[35] simultaneous measurement of clearances and amino acid excretion was avoided to exclude such a possibility. Blood urea nitrogen[36] was determined in fourteen of fifteen patients with renal disease.

RESULTS

The patterns of urinary amino acid excretion in normal subjects and in patients with renal disease during fasting and during infusion of 5 per cent aminosol are presented in Tables II and III, respectively. Renal functional measurements determined in fourteen of fifteen patients with renal disease (Table III) revealed a normal blood urea nitrogen (BUN) content in five (F. R., P. P., M. DeF., M. W., E. A.), slightly elevated values (20 mg.–40 mg./100 ml.) in five (M. M., H. B., M. D., M. P., A. D.), and markedly elevated levels (90 mg./100 ml. or greater) in four (J. F., S. M., J. L., E. R.). Glomerular filtration rate (inulin clearance), determined in four of five patients without azotemia, was normal in three (F. K., M. DeF., E. A.) and reduced in one (M. W.). Renal plasma flow (PAH clearance), measured in three of these patients (F. R., M. DeF., E. A.), was normal in all. Filtration and plasma flow were depressed proportionately in all four patients with azotemia in whom these values were determined. In one patient (E. S.), who was well except for pyuria, measurements of renal function were not made.

* We are indebted to Dr. Erwin Brand, Department of Biochemistry, Columbia University College of Physicians and Surgeons, for a generous supply of pure amino acids.

* Supplied through the courtesy of Dr. William Boger, Sharpe & Dohme, Inc., Glenolden, Pa.

TABLE II

FREE URINARY AMINO ACID EXCRETION IN NORMAL SUBJECTS DURING FASTING AND DURING 5 PER CENT AMINOSOL INFUSION*

Patient, Age and Sex	Period	Amino Acid													
		"Non-essential"							"Essential"						
		Aspartic Acid	Glutamic Acid	Glycine	α-alanine	Tyrosine	Glutamine†	Serine	Valine	Leucine and/or Isoleucine	Threonine	Histidine	Tryptophan	Methionine Sulfoxide	Lysine
A. R., 26, M	Fasting	0	++	++	0	0	++	0	0	0	0	0	0	0	0
	Infusion	++	+++	+++	++	0	++	++	0	0	0	0	0	+	0
A. B., 22, M	Fasting	0	+	+++	++	0	+	0	0	0	0	0	0	0	0
	Infusion	+++	+++	++++	++	0	+	0	++	0	0	0	0	+	0
L. B., 39, M	Fasting	0	0	++	0	0	0	0	0	0	0	0	0	0	0
	Infusion	++	++	+++	++	0	++	+	++	++	0	0	0	+	+
P. N., 31, M	Fasting	0	0	+++	++	0	++	0	0	0	0	0	0	0	0
	Infusion	0	++	++++	+++	0	+++	++	0	0	0	0	0	0	0
J. F., 15, M	Fasting	0	+	+++	++	0	0	0	0	0	0	0	0	0	0
	Infusion	+	++	++++	+++	0	++	++	0	0	0	0	0	0	0
N. A., 19, F	Fasting	0	++	+++	++	0	++	++	0	0	0	0	0	0	0
	Infusion	++	+++	+++	++	+	++	++	++	++	++	0	0	++	+
N. C., 27, F	Fasting	0	++	+++	+++	0	+++	0	++	++	0	+++	0	0	0
	Infusion	++++	++++	++++	+++	0	+++	0	+++	+++	0	+++	0	++	0
E. H., 19, M	Fasting	0	0	+++	++	0	++	++	+	0	0	+	0	0	0
	Infusion	+++	0	++++	+++	0	+++	+++	+++	+++	+	++	++	++	+++

* All urines were analyzed chromatographically and amino acid concentrations arbitrarily graded + to ++++, depending upon the spot size and color strength of the amino acid-ninhydrin complex. "Fasting" urines were collected prior to the administration of aminosol. Urine collected during infusion of approximately 500 ml. of 5 per cent aminosol is marked "infusion" and represents either a single sample in which the greatest hourly excretion occurred or a pooled specimen collected throughout the infusion.

† This amine, although properly not an amino acid, will be so considered throughout this study for purposes of simplicity.

TABLE III

FREE URINARY AMINO ACID EXCRETION IN PATIENTS WITH RENAL DISEASE DURING FASTING AND DURING 5 PER CENT AMINOSOL INFUSION*

Patient, Age and Sex with Diagnosis	BUN (mg. %)	GFR (ml./min.)	RPF (ml./min.)	FF (%)	Period	Amino Acid															
						"Non-essential"									"Essential"						
						Aspartic Acid	Glutamic Acid	Glycine	α-Alanine	Tyrosine	Glutamine	Serine	Proline	β-amino Isobutyric Acid	Valine	Leucine-Isoleucine	Threonine	Histidine	Tryptophan	Methionine Sulfoxide	Lysine	Arginine
F. R., 19, M Chronic pyelonephritis	9	112	622	18	Fasting	0	0	++++	+++	0	+++	0	0	0	0	0	0	0	0	0	0
					Infusion	0	++	+++	0	0	0	0	0	0	0	0	0	0	0	0	0
E. S., 18, F Acute pyelonephritis	...	...	...	..	Fasting	0	0	+++	++	0	+	0	0	0	0	0	0	+	0	0	0
					Infusion	++	0	++++	+++	+	+++	+++	0	0	++	++	+++	++	++	++	0
P. P., 36, F Chronic pyelonephritis	12	...	...	..	Fasting	0	0	+++	+++	0	+++	0	0	+++	++	0	0	0	0	0	0
					Infusion	++	++	+++	+++	0	+++	0	0	++	++	0	0	0	0	++	0
M. deF., 52, F Milkman's syndrome	16	83	572	15	Fasting	0	0	+++	++	0	++	0	0	0	+	+	0	+	0	0	0
					Infusion	0	++	++++	+++	0	+++	++	0	0	++	++	0	++	0	0	0
M. W., 64, F Chronic pyelonephritis	17	58	...	..	Fasting	0	0	++	++	0	+	0	0	0	+	+	0	0	0	0	0
					Infusion	0	++	++	++	0	0	0	0	0	++	++	0	0	0	++	0
E. A., 48, M Acute glomerulonephritis	19	150	541	28	Fasting	0	0	+++	+++	0	+++	+++	0	0	0	0	0	0	0	0	0
					Infusion	0	+++	++++	++++	0	+++	++++	0	0	0	+++	0	0	0	0	0
M. M., 22, F Chronic glomerulonephritis	26	58	400	15	Fasting	0	0	+++	++	0	++	0	+	0	+	0	0	0	0	+	0
					Infusion	++	0	++++	+++	0	+++	+++	+	0	++	++	0	++	0	+	++	0
H. B., 43, M Malignant nephrosclerosis	26	...	...	..	Fasting	0	0	+++	+++	0	+++	0	0	0	+	0	0	0	0	0	++
					Infusion	++	++++	++++	++++	0	+++	++	0	0	+++	++	0	0	0	0	+++
M. D., 43, F Disseminated lupus erythematosus	35	31	229	14	Fasting	0	0	++	++	0	0	0	0	0	0	0	0	0	0	0	0
					Infusion	0	++	+++	++	0	++	++	0	0	+	0	0	0	0	+	0
M. P., 38, F Chronic glomerulonephritis	40	...	...	..	Fasting	0	0	+++	++	0	0	0	0	0	0	0	0	0	0	0	0
					Infusion	0	+++	++++	+++	0	++	++	0	0	++	++	0	0	0	++	0
A. D., 53, M Benign nephrosclerosis	40	...	...	..	Fasting	0	0	+++	++	0	++	++	0	+++	+	+	0	0	0	0	0
					Infusion	0	+	+++	++	0	++	+++	0	+++	++	+++	0	0	0	0	0
J. F., 57, M Chronic glomerulonephritis	90	20	105	19	Fasting	0	0	+	+	0	+	+	0	0	0	0	0	0	0	0	0
					Infusion	0	0	++	++	0	++	+	0	0	0	0	0	0	0	0	0
S. M., 62, M Chronic pyelonephritis	97	...	...	..	Fasting	0	+	++	++	0	0	0	0	0	0	0	0	0	0	0	0
					Infusion	+	0	++	++	0	0	0	0	0	0	0	0	0	0	+	0
J. L., 22, M Chronic glomerulonephritis	111	7	42	17	Fasting	0	0	++	++	0	++	0	0	0	0	0	0	0	0	0	0
					Infusion	0	0	++	++	0	++	++	0	0	0	0	0	0	0	0	0
E. R., 40, M CCl_4 poisoning	160	...	...	..	Fasting	+	+	++	++	0	++	+	0	0	0	0	0	0	0	0	0
					Infusion	0	++	++	++	0	+	++	0	0	+	+	0	0	0	0	0

* Data handled as in Table II. All clearance values are average of two or more periods except in M. W.; no correction has been made for body surface area. Abbreviations are as follows: BUN = blood urea nitrogen; GFR = glomerular filtration rate, inulin clearance (ml./min.); RPF = renal plasma flow, p-aminohippurate clearance (ml./min.); FF = filtration fraction—GFR/RPF (%).

Free Urinary Amino Acid Patterns during Fasting. The normal fasting urinary chromatogram (Table II) revealed from one to seven (on the average four [upper half, Fig. 1]) different free amino acids. Glycine, α-alanine, glutamine* and glutamic acid constituted the greater portion of different amino acids were detected and glycine α-alanine and glutamine usually appeared in greater concentration than other acids. Of the "essential" amino acids, valine, leucine (and/or isoleucine) and histidine were detected occasionally, as in normal subjects, and methionine

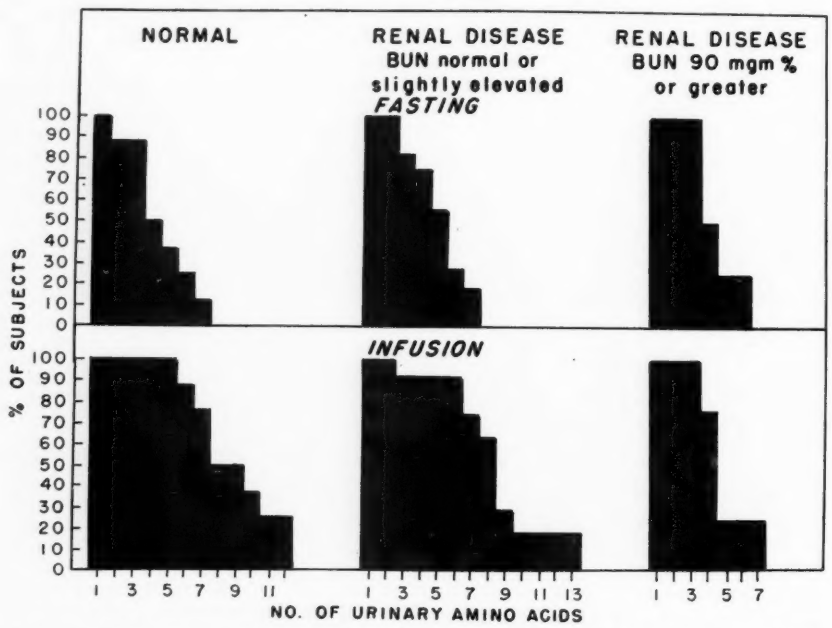

FIG. 1. Incidence of total number of free urinary amino acids determined chromatographically during fasting and during an infusion of approximately 500 ml. of 5 per cent aminosol in eight normal subjects, eleven patients with renal disease with a normal or slightly elevated blood urea nitrogen content (20–40 mg. per cent) and four patients with renal disease in severe renal insufficiency (blood urea nitrogen 90 mg. per cent or greater.) During fasting the number of detectable amino acids in patients with renal disease did not differ significantly from the normal. When aminosol was infused intravenously, patients without severe nitrogen retention responded normally with an increased output of amino acids, whereas few additional amino acids were lost in the urine of patients in advanced uremia.

amino acid output in most individuals. These "non-essential" acids tended to appear in greater concentration than "essential" amino acids, which were detected infrequently and in low concentration. Valine and histidine each appeared in two subjects and leucine (and/or isoleucine) in only one. Other "essential" amino acids were not excreted in detectable concentration.

Significant variations from the normal pattern were not encountered in patients with renal disease, irrespective of the nature of the underlying disease process or the degree of renal functional impairment. (Table III.) Two to seven (on the average four [upper half, Fig. 1])

* This amine, although properly not an amino acid, will be so considered throughout this study for purposes of simplicity.

sulfoxide, lysine and arginine rarely. It is apparent, therefore, that a defect in amino acid reabsorption was not demonstrable during fasting.

Free Urinary Amino Acid Patterns during Aminosol Infusion. The normal response to an infusion of 5 per cent aminosol consisted of a moderate increase in the number and concentration of free urinary amino acids. (Table II.) Since urine flow remained relatively constant, these changes are attributable to augmented amino acid excretion. A maximal excretion of twelve different acids was observed (lower half, Fig. 1) and, on the average, the concentration of eight different acids increased. Of the amino acids infused (Table I), glutamic acid, serine, glycine, α-alanine, aspartic acid, valine, methionine sulfoxide and leucine (and/or isoleucine)

were excreted in the largest amounts. Increased excretion of lysine and threonine occurred occasionally but little change in the output of arginine, phenylalanine, proline, histidine and tyrosine was noted, although these acids were infused in significant concentration. This phenomenon of selective amino acid reabsorption has been observed by others.[25]

Patients with renal disease without azotemia or with slight nitrogen retention (20 mg.–40 mg./100 ml.) responded normally to the infusion of aminosol. (Table III.) A maximal excretion of thirteen different amino acids occurred (lower half, Fig. 1) and, on the average, concentrations of six different amino acids increased. Urine flow was relatively constant. The character of the amino acids lost during infusion differed little from the normal. Small quantities of both "non-essential" and "essential" acids were excreted and in approximately the same relative concentrations as observed in normal subjects. Hence the capacity for reabsorption of an additional amino acid load appeared to be undisturbed.

In patients with severe renal functional impairment (BUN 90 mg./100 ml. or greater) few additional free amino acids were lost during aminosol infusion and little change from the "fasting" chromatogram was noted. A maximal excretion of seven different acids was observed and, as a rule, concentration of only two different amino acids increased. This response can be attributed to a severe depression of filtration since nitrogen retention was marked.

Conjugated or Bound Amino Acid Excretion. Hydrolysis of the "fasting" urine of normal subjects yielded increased and variable quantities of aspartic acid, glutamic acid, valine, leucine (and/or isoleucine), histidine, β-alanine, methionine sulfoxide, proline and serine. Little difference from the normal was encountered in patients with renal disease, regardless of the severity of functional impairment. When aminosol was administered to normal subjects, increased concentrations (when compared to hydrolyzed "fasting" urine) of aspartic and glutamic acids, lysine, arginine, threonine and tyrosine appeared in hydrolyzed urine. A similar increase in concentration of these acids was observed when urine of patients without azotemia or with slight nitrogen retention was hydrolyzed. However, in patients with severe uremia little change from the hydrolyzed "fasting" urine was noted. Hence both free and "bound" amino acids were retained to a greater than normal extent by these patients.

The increased quantities of amino acids yielded on hydrolysis may be attributed to the excretion of acetylated acids[30] and not to the presence of ninhydrin-reacting peptides since all color complexes were stable following acid hydrolysis.

DISCUSSION

A significant defect in amino acid reabsorption in patients with acute and chronic renal disease was not demonstrated in this study. The consistently normal urinary chromatographic patterns observed during fasting in all patients, irrespective of the nature of the underlying disease process or the degree of renal functional impairment, indicate that gross disturbance in amino acid output did not occur. Moreover, the capacity of the renal tubular cells for reabsorption of an additional load of amino acids provided by the infusion of aminosol appeared to be unaltered since less infusate was lost in the urine than in normals.

Abnormalities in urinary amino acid patterns were not encountered in those individuals in whom relatively excessive tubular dysfunction might have been expected, i.e., chronic pyelonephritis, carbon tetrachloride poisoning and Milkman's syndrome. Since aminoaciduria may be produced in animals by the tubulotoxic action of uranium,[37,38] it is of interest that chemical poisoning of the tubules by carbon tetrachloride in patient E. R. did not destroy the integrity of amino acid reabsorptive mechanisms. Although the degree and nature of the tubular damage induced in patient E. R. may not have been comparable to that produced by uranium, severe damage was evidenced by the marked nitrogen retention* and anuria. The failure to detect aminoaciduria in this patient at a time when tubular injury was undoubtedly marked implies that the capacity for amino acid reabsorption in man may be preserved in the presence of acute, widespread tubular injury.

However, transient aminoaciduria has been observed in acute renal failure following shock and hemorrhage during both the oliguric and recovery phases.[39] Moreover, excessive amino acid excretion has been described in a patient with renal failure due to phenol poison-

* It is likely that the blood urea nitrogen of 160 mg. % falsely reflected the degree of filtration depression at the time of this study since the patient was in a phase of rapid recovery from anuria.

ing.[40] These observations suggest that aminoaciduria may occur as a result of tubular injury, although the presence of a generalized disturbance in amino acid metabolism following shock and hemorrhage cannot be excluded since blood amino acid concentrations were not measured.

TABLE IV
URINARY CHROMATOGRAMS IN A PATIENT WITH FANCONI'S SYNDROME DURING FASTING AND DURING INFUSION OF 5 PER CENT AMINOSOL*

Amino Acid†	Fasting	During Infusion
Glycine	++++	++++
Glutamine	++++	++++
Serine	+++	+++
Asparagine	+++	++++
Tyrosine	+++	+++
α-Alanine	+++	++++
Histidine	++	++
Citrulline	++	+++
Valine	+++	++++
Leucine (and/or isoleucine)	+++	++++
Lysine	++	++
Methionine	.....	+++
Methionine sulfoxide	.....	++
Glutamic acid	.....	++

* Data handled as in Table II.

† Glutamine and asparagine are included but are properly amines. A 15 minute fasting urine was collected prior to the infusion of 5 per cent aminosol; 65 ml. of this solution were administered intravenously in 45 minutes, and urine collected during the last 15 minutes of infusion was analyzed. During aminosol infusion few additional amino acids were lost in the urine, a response that closely resembles the normal.

Although nitrogen retention was evident in many patients of this study, it is unlikely that a depression of glomerular filtration could entirely mask a defect in amino acid reabsorption since gross aminoaciduria may continue in Fanconi's syndrome despite a markedly reduced filtration rate and severe azotemia.[2–4] The finding of normal chromatographic patterns in these patients indicates that amino acid output may be maintained, and suggests that tubular reabsorption decreased roughly in proportion to filtration. This change in tubular activity may be attributable to an integration of glomerular and tubular functions (similar to the integration that occurs in uremia with respect to electrolyte and water excretion[41] rather than to a fundamental defect in reabsorption.

The amino acid patterns observed in normal persons and patients with renal disease differ strikingly from the grossly abnormal chromatograms of Fanconi's syndrome[3] and Wilson's disease.[11,32] This was evident in a chromatographic study (Table IV) of amino acid excretion in a three year old girl with the classic metabolic, chemical and skeletal abnormalities (Table V) of the Fanconi syndrome.* During fasting large

TABLE V
LABORATORY DATA IN A PATIENT WITH FANCONI'S SYNDROME

Serum

NPN (mg. %)	Calcium (mg. %)	Phosphorus (mg. %)	Bicarbonate (mEq./L.)	Chloride (mEq./L.)	Alkaline Phosphatase (B.U.)*
19.0	9.2	1.5	15.0	124	40.2

Urine

Specific Gravity	pH	Protein	Glucose	Microscopic
1.022	7.5	++	+++	Occ. WBC Occ. RBC.

X-ray
Rickets; multiple long bone fractures

* Bodansky units; normal, less than 4 units.

concentrations of eleven urinary amino acids were detected. Asparagine, tyrosine and citrulline, which are seldom seen in normal chromatograms, were present in abundance. When 70 ml. of 5 per cent aminosol were administered intravenously during a forty-five-minute period (equivalent of 450 ml. to a 70 kg. man), the urinary concentrations of some, but not all, amino acids increased and detectable amounts of glutamic acid and methionine appeared. A similarly normal response has been observed in Wilson's disease following the ingestion of protein foods or the intravenous infusion of protein hydrolysates[6] and in Fanconi's syndrome when methionine is given orally.[3] The ability to reabsorb a normal quantity of an additional amino acid load in the face of excessive excretion at normal plasma levels has been puzzling. Cooper et al.[6] contend that a constant functional or anatomic defect should result in a proportionately augmented urinary loss when increased loads are presented to the tubules. This would be

* We are grateful to Dr. Ruth Harris of Babies' Hospital for referring this patient to us.

true, however, only if the tubular defect were large. An abnormality involving only 5 to 10 per cent of the nephron population could account for the excessive aminoaciduria at normal plasma levels without altering appreciably the over-all capacity for increased reabsorption. In this respect the tubular abnormality may be likened to that postulated in renal glycosuria where the maximal glucose reabsorptive capacity is normal.[3,4] Moreover, the glycosuria of Fanconi's syndrome and Wilson's disease might also be attributable to a localized disturbance of reabsorption. This view may be supported by the demonstration of a normal maximal rate of glucose reabsorption (207 mg./min.) in the patient with Fanconi's syndrome reported in the present study.

Sufficient data are not available to permit accurate evaluation of the underlying renal disturbance in either Fanconi's syndrome or Wilson's disease. Despite the absence of clear-cut clinical or anatomic evidence of renal disease in hepatolenticular degeneration, renal functional impairment has been demonstrated. A moderate reduction of renal plasma flow without a change in glomerular filtration was reported by Hodges et al.[42] A more marked impairment of plasma flow accompanied by a proportionate reduction of filtration has been observed in two patients in this laboratory. The nature of this derangement is obscure, however, and characterization of the renal lesion must await further investigation.

Measurement of renal clearances in our patient with Fanconi's syndrome disclosed a normal* glomerular filtration rate (45 ml./min.) and renal plasma flow (120 ml./min.). From this and observations by others[2] it is apparent that renal function may be relatively undisturbed in the presence of discrete tubular defects. However, severe renal functional impairment may occur and death result from uremia.[2–4] The pathogenesis of this kidney disturbance is not known. Although underlying chronic pyelonephritis could account for many of the observed alterations in tubular function, the occasional disturbance in cystine metabolism and the frequent development of cirrhosis of the liver[2] point to a more widespread disorder. Furthermore, the failure to detect aminoaciduria in renal tubular acidosis and in the subjects of this study suggests that the capacity for reabsorption of amino acid by the tubules is not easily altered by tubular damage.

* No correction has been made for surface area. However, these values in a child weighing 8,900 gm. are sufficiently high to indicate that renal function was not altered significantly.

SUMMARY

Amino acid excretion was determined qualitatively in fifteen patients with acute and chronic renal disease and in eight normal subjects by paper partition chromatography. Significant defects in the capacity of the diseased renal tubule to reabsorb amino acids were not observed, either during fasting or when an additional amino acid load was provided by an infusion of fibrin hydrolysate. The urinary amino acid patterns in renal disease closely resembled the normal but differed strikingly from the gross aminoaciduria observed during fasting in a patient with the Fanconi syndrome in whom renal blood flow and filtration were undisturbed. During an infusion of fibrin hydrolysate a normal excretory response was elicited in this patient, suggesting that the defect in tubular reabsorption may involve a small percentage of the nephron population. No light is shed on the pathogenesis of the tubular lesion in Fanconi's syndrome, although the failure to detect aminoaciduria in patients with severe renal disease suggests that factors other than tubular damage may be involved.

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REFERENCES

1. Smith, H. W. The Kidney: Structure and Function in Health and Disease. New York, 1951. Oxford University Press.
2. McCune, D. J., Mason, H. H. and Clarke, H. T. Intractable hypophosphatemic rickets with renal glycosuria and acidosis (the Fanconi syndrome). *Am. J. Dis. Child.*, 65: 81, 1943.
3. Dent, C. E. The amino-aciduria in Fanconi syndrome. A study making extensive use of techniques based on paper partition chromatography. *Biochem. J.*, 41: 240, 1947.
4. Milne, M. D., Stanbury, S. W. and Thomson, A. E. Observations on the Fanconi syndrome and renal hyperchloremic acidosis in the adult. *Quart. J. Med.*, 21: 61, 1952.
5. Uzman, L. and Denny-Brown, D. Amino-aciduria in hepato-lenticular degeneration (Wilson's disease). *Am. J. M. Sc.*, 215: 599, 1948.
6. Cooper, A. M., Eckhardt, R. D., Faloon, W. W. and Davidson, C. S. Investigation of the amino-aciduria in Wilson's disease (hepatolenticular degeneration): demonstration of a defect in renal function. *J. Clin. Investigation*, 29: 265, 1950.
7. Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C., Jr. and Roos, A. Osteomalacia and late rickets. *Medicine*, 25: 399, 1946.

8. Pines, K. L. and Mudge, G. H. Renal tubular acidosis with osteomalacia: report of three cases. *Am. J. Med.*, 11: 302, 1951.
9. Latner, A. L. and Barnard, E. D. Idiopathic hyperchloremic renal acidosis in infants (nephrocalcinosis infantum). Observations on the site and nature of the lesion. *Quart. J. Med.*, 19: 285, 1950.
10. Levene, P. A. and Van Slyke, D. D. Gasometric determination of free and conjugated amino acids in the urine. *J. Biol. Chem.*, 12: 301, 1912.
11. Dent, C. E. Chromatographic studies. *Tr. Conf. Liver Injury*, 1: 53, 1947.
12. Frankl, W., Martin, H. and Dunn, M. S. The apparent concentration of free tryptophan, histidine and cystine in pathological human urine measured microbiologically. *Arch. Biochem.*, 13: 103, 1947.
13. de Vries, A. and Alexander, B. Studies on amino acid metabolism. II. Blood glycine and total amino acids in various pathological conditions, with observations on the effects of intravenously administered glycine. *J. Clin. Investigation*, 27: 655, 1948.
14. Kirk, E. The ability of nephritic patients to deaminize and form urea from ingested glycine. *J. Clin. Investigation*, 24: 136, 1945.
15. Christensen, H. N., Decker, D. G., Lynch, E. L., Mackenzie, T. M. and Powers, J. H. The conjugated, non-protein, amino acids of plasma. V. A study of the clinical significance of peptidemia. *J. Clin. Investigation*, 26: 853, 1947.
16. Lyttle, J. D., Goettsch, E., Greely, D. M., Grim, W. M. and Dunbar, P. Amino acid studies. II. Plasma amino acid retention as evidence of impaired liver function. Investigations in children with nephrosis and liver diseases. *J. Clin. Investigation*, 22: 169, 1943.
17. Kirk, E. Amino nitrogen changes of the blood in nephritis. *J. Clin. Investigation*, 12: 1091, 1933.
18. Berglund, H. Nitrogen retention in chronic interstitial nephritis and its clinical significance. *J. A. M. A.*, 79: 1375, 1922.
19. Blau, N. F. The amino acid nitrogen of the blood. I. The total free amino nitrogen in blood. *J. Biol. Chem.*, 56: 861, 1923.
20. Farr, L. E. and MacFadyen, D. A. Hypoaminoacidemia in children with nephrotic crises. *Am. J. Dis. Child.*, 59: 782, 1940.
21. Farr, L. E. The intravenous administration of small doses of caseine hydrolysate to nephrotic children and its effect upon the nitrogen balance and plasma amino acid level. *J. Pediat.*, 16: 679, 1940.
22. Farr, L. E. Amino acid nitrogen in the urine of children with the nephrotic syndrome following intravenous amino acids. *Proc. Soc. Exper. Biol. & Med.*, 42: 444, 1939.
23. Squire, J. R. The nephrotic syndrome. *Brit. M. J.*, 2: 1389, 1953.
24. Frost, D. V. and Sandy, H. R. Partial acid hydrolysates of proteins. VI. Assay of liquid protein hydrolysates in protein-depleted rats. *J. Biol. Chem.*, 175: 635, 1948.
25. Eckhardt, R. D. and Davidson, C. S. Urinary excretion of amino acids following the rapid injection of a solution of amino acids in man. *J. Clin. Investigation*, 20: 727, 1948.
26. Smyth, C. J., Levey, S. and Lesichak, A. G. The effects of the rate of administration of amino acid preparations on urinary wastage of amino acid nitrogen in man. *J. Clin. Investigation*, 27: 412, 1948.
27. Williams, R. J. and Kirby, H. Paper chromatography using capillary ascent. *Science*, 107: 481, 1948.
28. Datta, S. P., Dent, C. E. and Harris, H. An apparatus for the simultaneous production of many two-dimensional paper chromatograms. *Science*, 112: 621, 1950.
29. Dent, C. E. and Schilling, J. A. Studies on the absorption of proteins: the amino acid pattern in the portal blood. *Biochem. J.*, 44: 318, 1949.
30. Dent, C. E. A study of the behaviour of some sixty amino acids and other ninhydrin-reacting substances on phenol-"collidine" filter chromatograms, with notes as to the occurrence of some of them in biological fluids. *Biochem. J.*, 43: 169, 1948.
31. Biochemical Institute. Biochemical Institute Studies. IV. Individual metabolic patterns and human disease: An exploratory study utilizing predominately paper chromatographic methods. Austin, 1951. Univ. of Texas.
32. de Verdier, C. Paper chromatographic analysis of amino acid excretion in Wilson's disease. *Acta med. Scandinav.*, 138: 344, 1950.
33. Goldring, W. and Chasis, H. Hypertension and Hypertensive Disease. New York, 1944. The Commonwealth Fund.
34. Bradley, S. E., Bradley, G. P., Tyson, C. J., Curry, J. J. and Blake, W. D. Renal function in renal diseases. *Am. J. Med.*, 9: 766, 1950.
35. Lotspeich, W. D. and Pitts, R. F. The role of amino acids in the renal tubular secretion of ammonia. *J. Biol. Chem.*, 168: 611, 1947.
36. Gentzkow, C. J. An accurate method for the determination of blood urea nitrogen by direct Nesslerization. *J. Biol. Chem.*, 143: 531, 1942.
37. Rothstein, A. and Berke, H. Amino aciduria in uranium poisoning. I. The use of the amino-acid nitrogen to creatinine ratio in "spot" samples of urine. *J. Pharmacol. & Exper. Therap.*, 95: 179, 1949.
38. Berke, H. and Rothstein, A. Amino aciduria in uranium poisoning. II. The response of different amounts of uranium given intravenously and by inhalation. *J. Pharmacol. & Exper. Therap.*, 95: 198, 1949.
39. Lowe, K. G., Moodie, G. and Thomson, M. B. Glycosuria in acute tubular necrosis. *Clin. Sc.*, 13: 187, 1954.
40. Spencer, A. G. and Franglen, G. T. Gross aminoaciduria following a lysol burn. *Lancet*, 1: 190, 1952.
41. Nickel, J. F., Lowrance, P. B., Leifer, E. and Bradley, S. E. Renal function, electrolyte excretion and body fluids in patients with chronic renal insufficiency before and after sodium deprivation. *J. Clin. Investigation*, 32: 68, 1953.
42. Hodges, R. E., Kirkendall, W. M., Schwartz, C. and Wild, J. B. Some aspects of kidney function in hepatolenticular degeneration (Wilson's disease). *J. Clin. Investigation*, 33: 942, 1954.

Diuretic Action of Benemid*

Its Effect upon the Urinary Excretion of Sodium, Chloride, Potassium and Water in Edematous Subjects

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BENEMID,® p-(di-n-propyl-sulfamyl) benzoic acid, (probenecid), has been demonstrated to inhibit renal tubular secretion of penicillin,[1–4] p-aminohippurate,[4,7] phenolsulfonphthalein[4] and p-aminosalicylic acid.[1,5,6] It has also been shown to enhance the renal excretion of urate by inhibition of its tubular reabsorption.[8–14] Further, Schneider and Corcoran found in an instance of obscure hyperphosphatemia[15] that benemid depressed tubular reabsorption of phosphate, causing phosphaturia and lowering of elevated serum phosphate levels. In patients with hypoparathyroidism significant phosphate diuresis has likewise been induced.[16]

In our studies of patients with gout and with hypoparathyroidism the administration of benemid was observed to be followed by a twofold increase in urinary volume. Since the uricosuric action of benemid is most pronounced in gouty subjects with hyperuricemia, and its phosphaturic effect is most marked in hypoparathyroid subjects with hyperphosphatemia, it appeared desirable to investigate the diuretic action of benemid in subjects with sodium retention and edema.

Initial studies by Beyer[4] showed no effect of benemid on the renal excretion of sodium or chloride in the dog. Sirota et al.[13] studied renal clearances in non-edematous gouty subjects, using a 2 gm. dose. In acute experiments these investigators found significant but slight increases in the clearance of either sodium or chloride in five of twelve subjects. In a thirteenth gouty subject a four-day study of twenty-four-hour sodium and chloride excretion failed to show significant change. However, Sirota et al. pointed out that the water load given to maintain high levels of control urine flow may have masked a water diuretic effect. Moreover, the finding of only slight increase in clearance of sodium or chloride may be related to the fact that non-edematous subjects were studied. In addition the smaller (2 gm.) dose of benemid used may be insufficient to elicit a maximal diuretic response. In studies of gouty subjects Gutman and Yü[9] observed that the uricosuric effect, most marked in the first day or two, was usually associated with a marked water diuresis.

In the present study the effect of benemid on the urinary excretion of water, sodium, chloride and potassium, and on the concentration of serum electrolytes, was investigated in edematous patients.

CLINICAL MATERIAL AND METHODS

Twenty-six patients from the wards of Cook County Hospital served as subjects; all were edematous except one. Subjects with edema due primarily to causes other than congestive heart failure were excluded.

Thirteen subjects had congestive heart failure uncomplicated by hepatic or renal disease and without electrolyte disturbances. Three additional subjects had congestive failure associated with low levels of urinary sodium excretion (but with normal serum sodium concentration). Three others had congestive failure with hyponatremia as well as hyponatruria. Three had congestive failure with evidence of renal damage without azotemia, of whom one also had chronic gouty arthritis and hyperuricemia. In one subject congestive failure was complicated by hepatic disease. One subject with compensated organic heart disease was studied in an edema-

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free state. In addition, two subjects with cirrhosis and normal cardiac status were studied; one of these was hyponatremic.

In each subject serum non-protein nitrogen, total protein, sodium, potassium, chloride and carbon-dioxide combining power were determined. Hepatic tests were carried out if indicated. Each patient had twelve-hour urine concentration and phenolsulphonphthalein excretion tests prior to study.

All patients were kept at bed rest and all except one (Case 4) were completely digitalized. No mercurial diuretics were administered for five days prior to study. Water was allowed ad libitum and its intake estimated. The estimated fluid intake did not vary significantly throughout the period of study. The studies were conducted on open medical wards without metabolic study facilities. The diet given was the hospital low sodium diet, calculated to offer approximately 9 mEq. (200 mg.) of sodium. A preliminary period of observation on this regimen, varying from three to ten days, served to exclude subjects in whom spontaneous diuresis occurred. Biochemical study was initiated only after it was ascertained that clinical status, edema, weight and urinary output had stabilized.

TABLE 1

EFFECT OF BENEMID ON URINARY EXCRETION OF WATER, SODIUM AND CHLORIDE IN UNCOMPLICATED CONGESTIVE HEART FAILURE

Case No.	Patient, Race, Sex, Age, Diagnosis	Urinary Volume (cc./24 hr.)			Urinary Sodium (mEq./24 hr.)			Urinary Chloride (mEq./24 hr.)			Urinary Potassium (mEq./24 hr.)			Weight (lb.)		
		Mean Control	Maximal Output	Increment	Mean Control	Maximal Output	Increment	Mean Control	Maximal Output	Increment	Mean Control	Maximal Output	Increment	Mean Control	Maximum	Loss
1	W. C., N, M, 36, SHD	1,465	3,850	2,385	78	259	181	82	246	164	30	64	34	148	136	12
2	M. L., N, M, 57, ASHD	980	3,880	2,900	30	184	154	36	149	113	22	38	16	170	161	9
3	L. B., W, M, 35, RHD	1,730	2,190	460	50	131	81	59	151	92	54	86	32	158	151	7
4	R. L., N, M, 48, ASHD	625	1,300	675	26	90	64	43	77	34	15	26	11	185	181	4
5	M. H., W, M, 45, RHD, healed SBE	1,150	3,200	2,050	34	157	123	41	136	96	26	45	19	143	138	5
6	O. D., N, M, 61, ASHD	690	1,630	940	60	123	63	58	113	55	16	27	11	164	148	16
7	L. H., N, M, 38, RHD	3,100	3,900	800	39	96	57	85	145	60	27	37	10	188	182	6
8	M. F., N, F, 46, RHD	1,880	3,680	1,800	61	172	111	70	163	93	28	39	11	166	159	7
9	M. P., N, M, 32, HCVD	780	1,900	1,120	36	102	66	34	115	81	39	60	21	184	182	2
10*	E. Z., W, M, 59, ASHD	2,100	3,100	1,000	43	191	148	87	163	76	48	60	12	132	124	8
11	T. P., W, M, 75, HCVD	1,250	2,250	1,000	109	152	43	109	166	57	30	40	10	155	145	10
12	D. I., N, M, 47, ASHD	1,200	1,900	700	20	63	43	19	46	27	50	58	8	290	290	0
13	A. S., W, M, 65, ASHD	1,860	3,350	1,490	67	113	46	74	112	38	55	86	31	192	187	5

* 90 mEq. sodium diet.
W = white
N = Negro
SHD = syphilitic heart disease
ASHD = arteriosclerotic heart disease
RHD = rheumatic heart disease
HCVD = hypertensive cardiovascular disease

The test period consisted of two days of control observation, three successive days during which benemid was administered in divided oral doses of 4 gm. daily, and one or two subsequent control days. In five instances 4 gm. of benemid was given on only the third and fifth day of the test period, and in one the patient inadvertently received doses of 4, 2 and 2 gm. on the three successive days.

All urine was collected during each twenty-four-hour test period. Determinations of concentration of electrolytes in urine and serum were made daily. The weight was recorded daily. In most instances venous pressure was measured prior to benemid administration and at the end

of the test period. Clinical status, including observations on pulse rate, pulmonary rales, hepatomegaly and edema, was noted daily.

Following the test period a comparison of benemid- and mercurial-induced diuresis was made in most subjects in terms of weight loss, urinary output and clinical response, and in seven instances urine and serum electrolyte concentrations were determined.

TABLE II

DIURETIC EFFECT OF BENEMID IN THIRTEEN PATIENTS WITH UNCOMPLICATED CONGESTIVE HEART FAILURE

	Control Period Mean	Test Period Maximal	Increment
Urine:			
Volume, cc./24 hr.	1,450 (620–3,100)	2,780 (1,300–3,900)	1,330 (460–2,900)
Sodium, mEq./24 hr.	50 (20–109)	141 (63–259)	91 (43–181)
Chloride, mEq./24 hr.	61 (19–109)	137 (24–246)	76 (27–164)
Potassium, mEq./24 hr.	34 (15–55)	51 (26–86)	17 (8–34)
Mean weight loss:			
Pounds		7 (0–16)	

RESULTS

Uncomplicated Congestive Heart Failure. In thirteen patients with congestive heart failure uncomplicated by hepatic or renal disease, and with normal serum and urinary electrolyte values, a significant diuresis of water, sodium and chloride was observed following benemid administration. (Subjects 1 to 13, Table I.) In the twenty-four-hour period of maximal response to benemid the mean increment in excretion of water in excess of the mean twenty-four-hour control volume was 1,330 cc. (range 460 cc. to 2,900 cc.); the premedication urinary volume was approximately doubled. The mean increment in sodium excretion in excess of the control values was 91 mEq. (range 43 to 181 mEq.); thus the urinary sodium excretion increased threefold. The mean increment in chloride excretion of 76 mEq. (range 27 to 164 mEq.) resulted from a twofold increase of the mean control values. The mean increment in potassium excretion was 17 mEq., above a mean control value of 34 mEq./24 hours; this was considered to be of doubtful significance. The mean weight loss for the group was 7 pounds (range 0 to 16 pounds) at the end of the seven-day test period. (Table II.) Figure 1 (W. C.) illustrates a typical maximal diuretic response, with close parallelism of augmented water, sodium and chloride excretion.

The maximal response with respect to day of drug administration was variable. In seven instances the maximal urinary output occurred

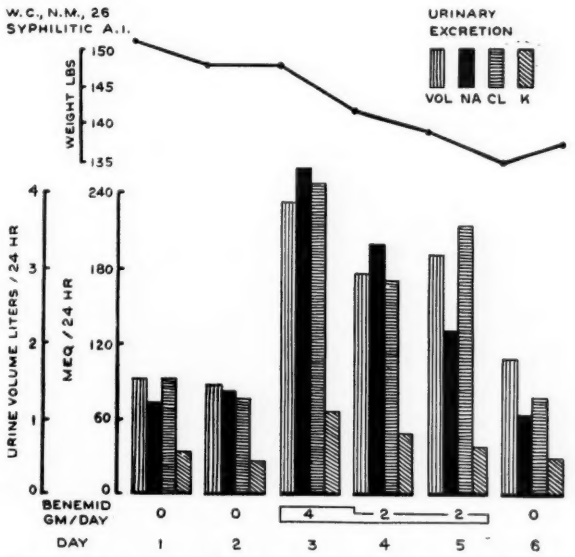

FIG. 1. Total twenty-four-hour urinary excretion of water, sodium, chloride and potassium in subject W. C., showing a maximal diuretic response. Following cessation of benemid, urinary volume and solutes returned to control values and weight rose.

on the first day, in four instances on the second day, and in two instances water diuresis occurred on the day after benemid was discontinued. The increase of sodium and chloride excretion occurred simultaneously in all cases; in five instances on the first day, in six on the second day, in one case on the third day and in one instance on the day following withdrawal of benemid. Thus in all but two instances the maximal diuresis of water, sodium and chloride occurred simultaneously, i.e., within the same twenty-four-hour period.

In all instances of diuretic response the concentration of serum sodium, chloride and potassium showed no change during the relatively short period of study. In two instances discontinuous administration after variable rest periods in excess of four days resulted in a repetition of the diuretic response, without alteration of serum sodium concentrations.

The concentration of urinary sodium and chloride significantly increased, despite rise in urinary volume, in eleven of the thirteen instances of uncomplicated congestive heart failure. A dissociation of water from sodium and

chloride response occurred in two instances; no significant change in urinary volume occurred, however, a rise in urinary concentration of sodium and chloride led to a twofold increase in sodium and chloride excretion. This dissociated response is charted in Figure 2 for subject L. B.

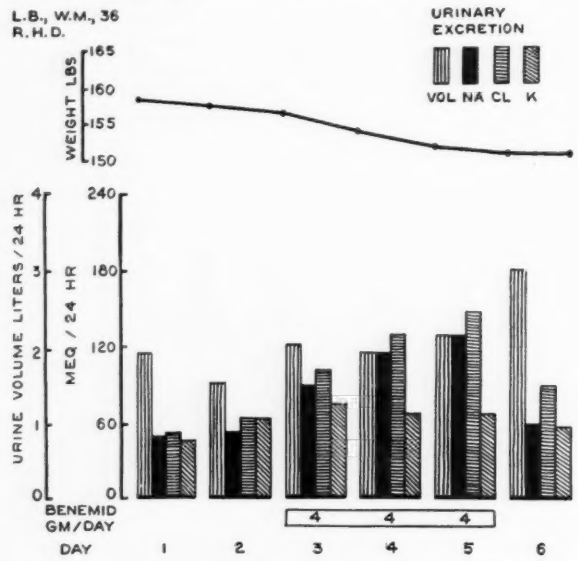

FIG. 2. Total twenty-four-hour urinary excretion of water, sodium, chloride and potassium in subject L. B., showing augmentation of urinary solutes but not of water.

Coexistent Gout and Congestive Heart Failure. In one subject with arteriosclerotic heart disease, congestive heart failure and chronic gouty arthritis with hyperuricemia (subject 23, J. K.) the simultaneous effect of benemid on urate, water, sodium and chloride excretion was studied. (Fig. 3.) The serum uric acid level was lowered and urinary urate excretion rose. No change in urinary sodium or chloride concentration occurred but a twofold increase of urinary volume was accompanied by a parallel increment in twenty-four-hour sodium and chloride excretion. This response was not anticipated in the face of evidence of impaired renal function (phenolsulphonphthalein excretion of 35 per cent in two hours, non-protein nitrogen 47 mg./100 cc. and non-visualization of left kidney).

Failure of Diuretic Response. Twelve subjects failed to respond to benemid with augmented excretion of sodium and chloride. (Table III.) Oliguria was prominent in nine of the failures to respond. This was commonly associated with low urinary sodium and chloride concentration in the twenty-four-hour control periods. In five of these cases the twenty-four-hour urinary sodium excretion was less than 3 mEq., and in two others the total was less than 12 mEq.

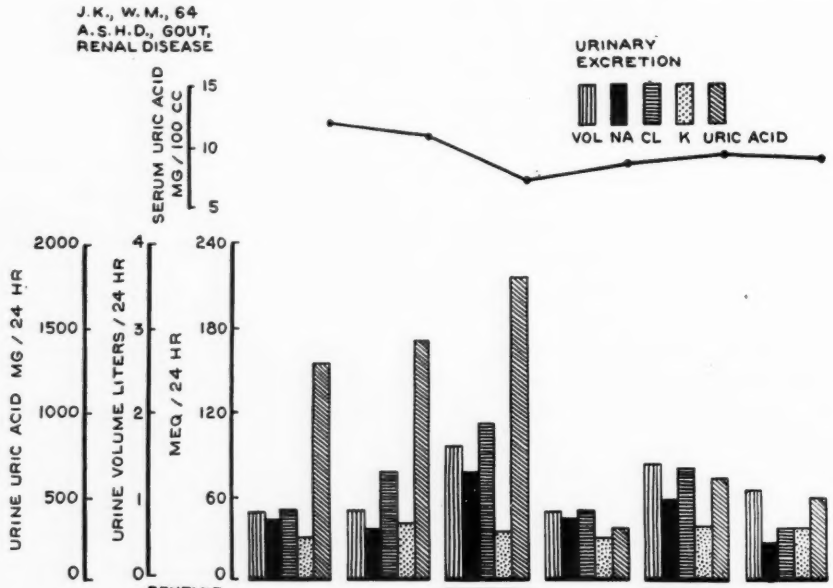

FIG. 3. Total twenty-four-hour urinary excretion of water, sodium, chloride, potassium and uric acid in subject J. K., showing simultaneous uricosuric and diuretic effect of benemid. Increased urate excretion accompanied fall in serum uric acid. Twofold increment of sodium and chloride excretion resulted from water diuresis without increased urinary concentration of sodium and chloride.

A potassium diuresis occurred in two patients (Nos. 20 and 26) associated with significant water diuresis (increments of 1,400 and 1,300 cc.). This was not accompanied by increased excretion of sodium or chloride; in fact, the control excretion of both was moderately low (less than 30 mEq./24 hr.).

Water diuresis alone occurred in seven of the twelve subjects; an augmented excretion of dilute urine occurred without change in twenty-four-hour urinary sodium and chloride excretion; in fact the concentration of urinary sodium and chloride fell progressively. Such a response is charted for patient S. B. in Figure 4. Thus water diuresis occurred in a total of twenty-one of the twenty-six subjects studied. In the remaining five subjects the total failure of diuretic response was associated with: (1) prior loss of edema (No. 16), (2) complicating hepatic disease (No. 24), (3) hyponatruria (No. 17) and (4) renal disease (Nos. 21 and 22).

TABLE III

EFFECT OF BENEMID ON URINARY EXCRETION OF WATER, SODIUM AND CHLORIDE IN SUBJECTS WITH HYPONATREMIA, HYPONATRURIA, RENAL AND HEPATIC DISEASE

Case No.	Patient, Race, Sex, Age, Diagnosis	Urinary Volume (cc./24 hr.)			Urinary Sodium (mEq./24 hr.)			Urinary Chloride (mEq./24 hr.)			Urinary Potassium (mEq./24 hr.)			Weight (lb.)		
		Mean Control	Maximal Output	Increment	Mean Control	Maximal Output	Increment	Mean Control	Maximal Output	Increment	Mean Control	Maximal Output	Increment	Mean Control	Minimum	Loss
14	R. R., W, M, 49, HCVD	550	2,200	1,650	1	10	9	5	11	6	15	59	44	203	198	5
15	M. S., N, F, 43, RHD	600	1,700	1,100	2.5	5.3	2.8	6.5	14	8.5	26	49	23	222	223	+1
16*	F. S., W, F, 42, RHD	1,560	1,570	10	80	26	−54	55	35	−20	45	44	−1	105	101	4
17	P. J., N, F, 30, RHD	435	700	265	8	19	11	4	20	16	18	27	9	120	118	2
18	R. P., N, M, 69, ASHD, hyponatremia	1,850	3,000	1,150	1.6	5.4	3.8	3.5	12	8.5	17	33	16	153	152	1
19	S. B., W, M, 69, ASHD, hyponatremia	500	1,550	1,050	51	44	−7	4.1	10.7	6.6	22	27	5	177	173	4
20	J. S., W, M, 48, ASHD, hyponatremia	1,900	3,300	1,400	1.0	1.0	0	27	26	−1	53	117	64	221	215	6
21	S. S., N, M, 48, RHD, chronic nephritis	680	580	−100	23	27	4	6	32	26	21	31	10	145	141	4
22	C. M., W, M, 65, ASHD, nephrosclerosis	1,200	1,440	240	78	65	−13	94	86	−8	49	62	13	120	121	+1
23	J. K., W, M, 64, ASHD, gout, nephrosclerosis	750	1,610	860	38	77	39	63	111	48	35	43	8	150	149	1
24	N. B., W, M, 58, Laennec's cirrhosis, ASHD	810	1,140	330	29	25	−4	32	24	−8	39	46	7	146	145	1
25	P. D., W, M, 48, Laennec's cirrhosis, hyponatremia	500	1,150	650	0.3	0.8	0.5	5	12	7	21	36	15	225	227	+2
26	C. D., W, M, 42, Laennec's cirrhosis	650	1,950	1,300	12	18	6	13	36	23	42	176	134	196	194	2

* Free of edema.

Clinical Effect. In eleven of thirteen instances successful diuresis was accompanied by an improvement in clinical status of the patient during the seven day period of study, manifested by diminution of edema, pulmonary rales, hepatomegaly and decrease in venous pressure. In general, satisfactory clinical response ultimately followed significant diuretic response. Clinically, diuresis with benemid did not produce the marked urgency and increase in frequency seen with mercurials. Rather there was a polyuria characterized by a moderate increase in frequency, nocturia and passage of a large volume with each micturition.

Side Effects. In the dosage administered no gastrointestinal symptoms or evidence of renal or other toxicity was noted.

Comparison with Mercurial Diuretics. An accurate comparison of the response to benemid and to mercuhydrin is difficult because of the irregularity of diuretic response, which is

dependent on differing amounts of retained edema fluid. In seven instances comparison of the biochemical response indicated greater water and electrolyte response to benemid in three cases, to mercuhydrin in three cases and

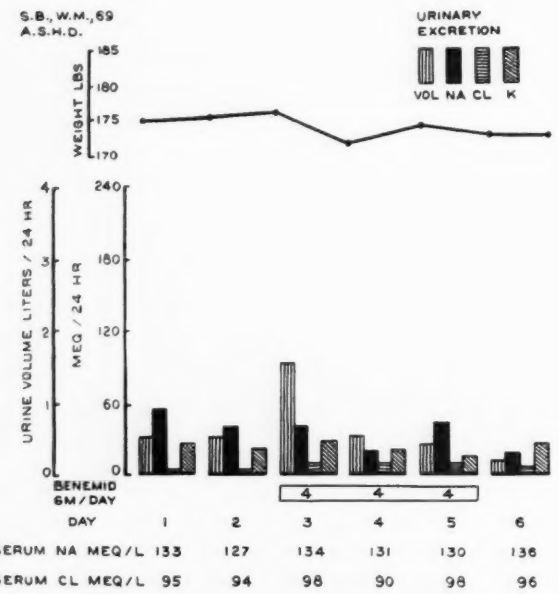

FIG. 4. Total twenty-four-hour urinary excretion of water, sodium, chloride and potassium in subject S. B., showing augmented water excretion with fall in total twenty-four-hour solute excretion, in the presence of hyponatremia and hyponatruria.

to neither in one instance. Comparison of weight loss and urinary output in twenty-three instances indicated somewhat greater responsiveness to mercuhydrin in ten, equal response in eight and somewhat greater response to benemid in five instances. With benemid-induced diuresis sodium was excreted somewhat in excess of chloride in over half of thirteen subjects. In no case was chloride diuresis alone induced, as is so frequently observed following mercurial diuresis.[17,18]

Inhibition of Benemid Effect by Salicylate. The uricosuric effect of benemid is inhibited by salicylate.[9,14] In one subject (Fig. 5) an attempt was made to demonstrate salicylate inhibition of the diuretic effect of benemid. After diuresis was demonstrated to occur with benemid, salicylate was given and subsequent administration of benemid, in the presence of an elevated serum salicylate level, failed to elicit diuretic response. Administration of a third course of benemid again elicited diuretic response which was promptly eliminated by a new rise in serum salicylate level. In a second subject benemid-induced diuresis and uricosuria were interrupted by administration of salicylate (blood level 30 mg./100 cc.) and diuresis and uricosuria resumed following salicylate withdrawal.

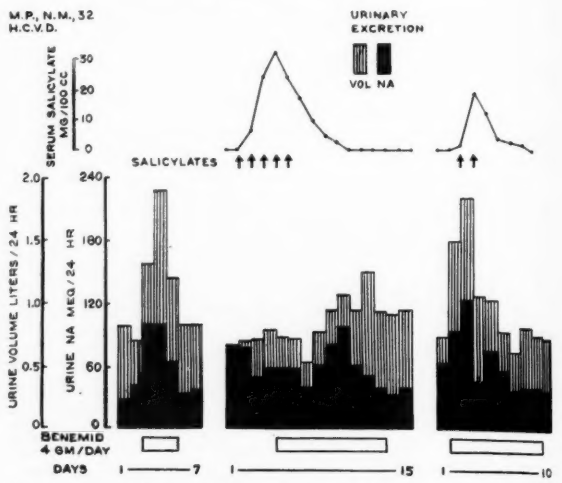

FIG. 5. Total twenty-four-hour urinary excretion of water and sodium in three discontinuous periods in subject M. P. In the first, diuresis accompanied benemid administration. In the second, a high salicylate level prevented response to benemid. In the third period, newly induced benemid diuresis was checked and eliminated by salicylate.

COMMENT

The results of the present study indicate a significant diuretic effect of benemid on the urinary excretion of water, sodium and chloride in some edematous subjects with congestive heart failure. No diuretic effect was observed in subjects with hyponatremia, hypochloremia or marked lowering of urinary sodium or chloride concentration. In some instances an increase in urinary volume was not accompanied by augmented excretion of sodium and chloride. In fact, in several instances administration of benemid resulted in a further reduction of already low twenty-four-hour urinary sodium and chloride excretion. Failure of diuretic response could in fact be predicted by the finding of a total twenty-four-hour urinary sodium or chloride excretion of less that 12 mEq. This is consistent with observations indicating a high reabsorptive capacity for sodium and chloride in the presence of salt depletion[19,20] and the known effect of serum chloride concentration on chloride reabsorption at the proximal tubule.[20,21] In no instance did hyponatremia result from benemid-induced diuresis. However, more prolonged administration of benemid, if

diuresis is sustained, might well result in salt depletion.

The long-term toxicity of benemid in high (4 gm.) doses given repetitively remains to be evaluated. In the experience of others[9] considerable gastrointestinal distress has accompanied the administration of doses in excess of 1 gm. The failure of diuretic response in the presence of hepatic disease is well recognized and remains unexplained.[23,28] It was not anticipated that benemid would necessarily induce diuresis in the presence of renal disease, since its action is predicated upon intact renal tubular function.

Although renal clearances were not determined in this study, Sirota et al. found no increase in glomerular filtration rate in thirteen non-edematous gouty subjects.[13] It seems reasonable to assume that the observed increased excretion of water, sodium and chloride is the result of an alteration in reabsorption of these substances rather than increased glomerular filtration.

It is accepted that benemid inhibits tubular transport mechanisms responsible for the renal tubular secretion of penicillin, phenolsulfonphthalein, p-aminohippurate and p-aminosalicylic acid.[4] It was initially believed that the benemid effect on the secretory functions of the renal tubule is highly selective. However, its effect in decreasing tubular reabsorption of urate[13,24] and phosphate[15] has also been demonstrated. The augmented excretion of water, sodium and chloride induced by benemid is postulated in the present study to result also from diminished tubular reabsorption of these substances. The instances of excretion of a dilute urine (augmented water excretion without increment of solutes) must await further clarification.

SUMMARY

1. In thirteen subjects with uncomplicated congestive heart failure benemid in dosage of 4 gm. daily produced a significant diuretic response. The mean increment of water excreted on the day of maximal response was 1,330 cc., of sodium 91 mEq. and of chloride 76 mEq./24 hours. A fourteenth subject with associated gout and renal disease showed a lesser but significant response. Diuresis occurred in most instances on either the first or second day of drug administration.

2. Water diuresis without enhancement of sodium or chloride excretion occurred in seven other subjects. Failure of diuresis to occur in the remaining five subjects was associated with the presence of hepatic disease, renal disease, hyponatremia and hyponatruria.

3. It is postulated that benemid-induced diuresis is the result of decreased tubular reabsorption of water, sodium and chloride.

Acknowledgments: These studies were supported in part by a grant from the Dr. Leonard H. and Louis D. Weissman Medical Research Foundation. The benemid used was generously supplied by Sharp and Dohme, Inc.

REFERENCES

1. Boger, W. P., Beatty, J. O., Pitts, F. W. and Flippin, H. F. The influence of a new benzoic acid derivative on the metabolism of para-aminosalicylic acid (PAS) and penicillin. *Ann. Int. Med.*, 33: 18, 1950.
2. Beyer, K. H. Functional characteristics of renal transport mechanisms. *Pharm. Rev.*, 2: 227, 1950.
3. Burnell, J. M. and Kirby, W. M. Effectiveness of a new compound, benemid, in elevating serum penicillin concentrations. *J. Clin. Investigation*, 30: 697, 1951.
4. Beyer, K. H., Russo, H. F., Tillson, E. K., Miller, A. K., Verwey, W. F. and Gass, S. R. Benemid, p-(di-n-propyl-sulfamyl)-benzoic acid: its renal affinity and its elimination. *Am. J. Physiol.*, 166: 625, 1951.
5. Boger, W. P. and Pitts, F. W. Plasma concentrations of p-aminosalicylic acid (PAS) increased by p (di-n-propyl-sulfamyl)-benzoic acid. *Science*, 112: 149, 1950.
6. Boger, W. P., Pitts, F. W. and Gallagher, M. E. Benemid and carinamide: comparison of effect on para-aminosalicylic acid (PAS) plasma concentrations. *J. Lab. & Clin. Med.*, 36: 276, 1950.
7. Boger, W. P., Matteucci, W. V. and Schimmel, N. H. Renal clearances of penicillin, phenolsulphonphthalein (PSP) and para-aminohippurate (PAH) modified by Benemid. *Am. J. Med.*, 11: 517, 1951.
8. Gutman, A. B. *In* combined staff clinic on uric acid metabolism and gout. *Am. J. Med.*, 9: 799, 1950.
9. Gutman, A. B. and Yü, T. F. Benemid (p-(di-n-propylsulfamyl)-benzoic acid) as a uricosuric agent in chronic gouty arthritis. *Tr. A. Am. Physicians*, 64: 279, 1951.
10. Talbott, J. H., Bishop, C., Norcross, B. M. and Lochie, L. M. The clinical and metabolic effects of benemid in patients with gout. *Tr. A. Am. Physicians*, 64: 372, 1951.
11. Gutman, A. B. Gout, a derangement of purine metabolism. Advances Int. Med., vol. 5, p. 227. New York, 1952. Year Book Publishers, Inc.
12. Bishop, C., Rand, R. and Talbott, J. H. The effect of benemid (p-(di-n-propylsulfamyl)-benzoic acid) on uric acid metabolism in one normal and one gouty subject. *J. Clin. Investigation*, 30: 889, 1951.
13. Sirota, J. H., Yü, T. F. and Gutman, A. B. Effect of benemid (p-(di-n-propylsulfamyl)-benzoic acid)

on urate clearance and other discrete renal functions in gouty subjects. *J. Clin. Investigation*, 31: 692, 1952.

14. Pascale, L. R., Dubin, A and Hoffman, W. S. Therapeutic value of probenecid (benemid) in gout. *J. A. M. A.*, 149, 1188, 1952.
15. Schneider, R. W. and Corcoran, A. C. Familial nephrogenic osteopathy due to excessive tubular reabsorption of inorganic phosphate: a new syndrome and a novel mode of relief. *Proc. Central Soc. Clin. Research*, 23: 93, 1950.
16. Pascale, L. R., Dubin, A. and Hoffman, W. S. The influence of benemid on the urinary excretion of phosphate in hypoparathyroidism. In press.
17. Lesser, G. T., Dunning, M. F., Epstein, F. H. and Berger, E. Y. Mercurial diuresis in edematous individuals. *Circulation*, 5: 85, 1952.
18. Rice, L., Frieden, J. and Smith, M. Tubular action of mercurial diuretics. *Am. J. Physiol.*, 175: 47, 1953.
19. Frieden, J., Rice, L. and Elisberg, E. I. Renal tubular sodium metabolism in sodium deficiency states. *Am. J. Physiol.*, 168: 93, 1952.
20. Rice, L., Frieden, J., Kaplan, B. M. and Smith, M. Renal tubular resistance to mercurial action in sodium deficiency. *Am. J. Physiol.*, 175: 45, 1953.
21. Pullman, T. N. and McClure, W. W. Excretion of chloride and water in normal man. *Federation Proc.*, 10: 105, 1951.
22. Rapoport, S. and West, C. D. Ionic antogonism: effect of various anions on chloride excretion during osmotic diuresis in the dog. *Am. J. Physiol.*, 162: 668, 1950.
23. Ralli, E. P., Robson, J. S., Clarke, D. H. and Hoagland, C. L. Factors influencing ascites in patients with cirrhosis of the liver. *J. Clin. Investigation*, 24: 316, 1945.
24. Berliner, R. W., Hilton, J. G., Yü, T. F. and Kennedy, T. J., Jr., The renal mechanism for urate excretion in man. *J. Clin. Investigation*, 29: 396, 1950.
25. Mudge, G. H., Foulks, J. and Gilman, A. Effect of urea diuresis on renal excretion of electrolytes. *Am. J. Physiol.*, 158: 218, 1949.
26. Duggan, J. J. and Pitts, R. F. Site of action of mercurial diuretics. *Federation Proc.*, 8: 37, 1949.
27. Pitts, R. F. and Sartorius, O. W. Mechanism of action and therapeutic use of diuretics. *Pharm. Rev.*, 2: 161, 1950.
28. Stein, M., Schwartz, R. and Mirsky, I. A. The antidiuretic activity of plasma of patients with hepatic cirrhosis, congestive heart failure, hypertension and other clinical disorders. *J. Clin. Investigation*, 33: 77, 1954.

Reviews

Anatomy of the Glomerulus*

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The fine details of glomerular structure are poorly understood. Such problems as the relationship between glomerular endothelial and epithelial elements, the relative position and composition of the mesangium, and the relationship of the basement membrane of Bowman's capsule to the basement membrane of the glomerulus have remained unsolved even with the most refined technics of light microscopy. It is now possible to solve some of these problems with the use of the electron miscoscope. It is possible to obtain a general three-dimensional picture of the glomerulus utilizing electron and light microscopy upon thin plastic-embedded sections.

METHODS

In this study renal biopsies from dogs and human beings have been used. All specimens were obtained by biopsy either from dogs or patients without known renal disease; a few specimens from dogs were obtained immediately postmortem (five minutes). These slices were cut with a razor blade into cubes about 1 mm. in size and immediately dropped into a solution of 1 per cent osmium tetroxide buffered to pH 7.4 with Ringer's solution and veronal buffer.

After fixation in the osmic acid solution for two hours the blocks were dehydrated by successive transfers of fifteen minutes each through 70, 90 and 100 per cent alcohol, infiltrated with one-half methacrylate—one-half 100 per cent alcohol and then two changes of pure methacrylate (1:3 methyl:butyl methacrylate). Embedding was performed in a No. 3 gelatin capsule half-filled with methacrylate to which benzoyl-peroxide, 17 mg. per mL., was added to catalyze the hardening process. After drying twenty-four hours at 45°C., the capsules were dissolved from the plastic block which was then ready for sectioning. Thin sections were cut on a Minot-International rotary microtome with a glass knife.[1] These were then examined in an RCA Model EMU electron microscope. For phase microscopy we have utilized tissue fixed as described, embedded in methacrylate, cut at 0.5 to 1 micron and affixed to ordinary glass microscope slides. Some of these sections were examined directly with the phase microscope, while adjacent sections were treated with ammoniacal silver[2] after removal of the osmium and then examined with the light microscope. (Fig. 2C and D.)

RESULTS

The structures found in the glomerulus are: 1. Basement membrane of Bowman's capsule (BC). 2. Epithelium of Bowman's capsule. 3. Epithelium of the glomerulus (podocyte); (a) nucleus (PN), (b) cell body (PC), (c) foot process (PFP). 4. Basement membrane of the glomerulus (BG). 5. Endothelium of the glomerulus (endothelial cell); (a) nucleus (EN), (b) cell body (EC), (c) lining network (ELN). 6. The glomerulus stalk (mesangium) (M). 7. Capillary lumen (C). 8. Erythrocyte (RBC).

In Figure 1 are diagrammatic sketches presenting our concept of the over-all structure. In this illustration (*a*) demonstrates the way in which the basement membrane of the tubules expands as Bowman's capsule (BC), and then covers the capillary endothelium as the only basement membrane found in the glomerulus (BG). Hall[3] has called this structure the *lamina densa* but in view of its structural similarity with all other basement membranes in the body it seems preferable to us to continue to call it simply the basement membrane of the glomerulus. It corresponds to what is often labeled the visceral layer of the basement membrane of Bowman's capsule. The epithelium of Bowman's capsule is continuous with the interdigitating

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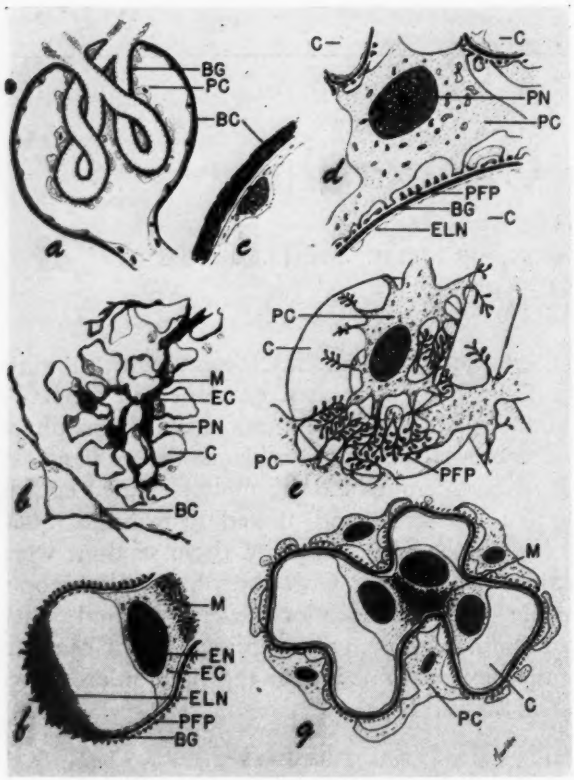


FIG. 1. Schematic representation of structures which comprise the glomerulus.

epithelial cells (podocytes, PC) of the glomerulus. These cells, called pericytes by Zimmerman,[4,5] are shown in (*d*).* A schematic view of their position on a twisting capillary, with foot processes that interdigitate with foot processes from other podocytes, is shown in (*e*). These foot processes (PFP) are applied to all external surfaces of the capillaries and it is between these foot processes that simple filtration probably occurs. A diagram of the cross section of an endothelial cell of the glomerulus can be noted in (*f*). Its nucleus (EN) is surrounded by the cell body proper (EC), whose cytoplasm is thinned out on one side to form the walls of the capillary lumen (C), and wherever this portion lies in close proximity to the basement membrane it is called the endothelial lining network (ELN). On cross section this portion occasionally appears as interrupted dashes, and on coronal section it occasionally has the appearance of "chicken wire" fencing. It is called the endothelial lining network in this paper. Hall[3] has labeled it the *lamina fenestrata* but since we are in doubt as to its truly fenestrated nature we prefer the term endothelial lining network. A longitudinal section of a glomerular lobule is shown at low power in (*b*). It depicts a central stalk of dense material (M) with which the capillary (C) always remains in contact as it repeatedly divides and reunites during its tortuous course into and out of the glomerulus. A diagram of a cross section of this stalk showing that it is comprised of a group of contiguous endothelial cells can be noted in (*g*). The external portions of this endothelial stalk (M) are hollowed out as the lumen of a capillary (C).

The Basement Membrane of Bowman's Capsule. The basement membrane of Bowman's capsule is continuous with the basement membrane of the proximal convoluted tubule. Bowman[6] saw this and stated that "the basement membrane of the uriniferous tube, expanded over the malpighian tuft to form its capsule, is a simple, homogeneous and perfectly transparent membrane, in which no structure can be discovered. It is perforated by the afferent and efferent vessels and is certainly not reflected over them." That the basement membrane was, indeed, reflected over the entering vessels was the view of Seng,[7] who in 1871 saw and demonstrated the continuity of the basement membrane of Bowman's capsule with that of the basement membrane of the glomerulus. Since then many observers have also held that the basement membrane of Bowman's capsule is reflected over the capillaries, much as the parietal peritoneum is reflected along the mesentery and over the small intestine.

The basement membrane of Bowman's capsule (BC), as seen in the electron microscope, is a structure about 3,500 to 5,000 Å thick, fairly dense when stained with osmium and having a laminated appearance. (Fig. 3A.) No other specific structural details have been observed in this membrane. It is continuous at one end with the basement membrane of the tubule and at the other end is directly continuous with the basement membrane of the glomerulus (BC). (Fig. 2D.) The basement membranes of Bowman's capsule of the dog and man appear identical.

Epithelium of Bowman's Capsule. Lying on the inside of the basement membrane of Bowman's capsule is a sheet of flattened epithelial cells. (Fig. 3B.) These were recognized by Drasch[8]

*Hall[3] has called these cells *podocytes* because of their peculiar foot processes. Since *pericyte* has the connotation of a pericapillary cell similar or identical to the Rouget cells of the capillaries, we believe that the name pericyte is not applicable to the cells found in the glomerulus and prefer Hall's terminology of *podocyte*.

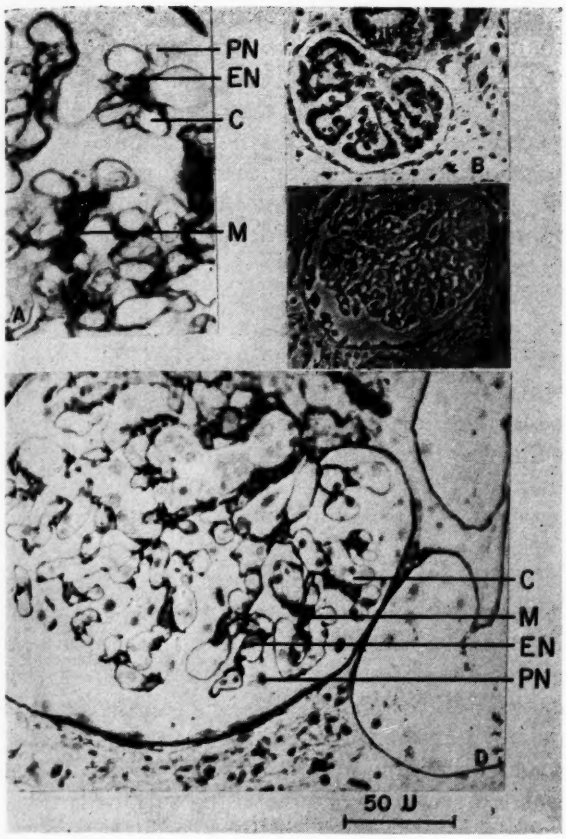


FIG. 2. The glomerulus as seen by light microscopy. A, a cross section (upper right) and longitudinal section of glomerular lobules. Basement membranes are stained with Schiff's periodic acid stain. This stain is specific for the basement membrane of the glomerulus. (Courtesy McManus, *Am. J. Path.*[20].) B, section of fetal glomerulus stained with hematoxylin and eosin. (Courtesy McMANUS, and Lea and Febiger[14].) C, section of glomerulus, fixed with osmic acid, embedded in methacrylate, cut at 0.5 micron and viewed with phase microscopy. D, adjacent sections of same glomerulus shown in C. The basement membrane is stained with silver (Wilder[2]) and the section viewed with direct transmitted light. The cellular material appears indistinct because of its thinness, and the basement membrane stands out prominently (human).

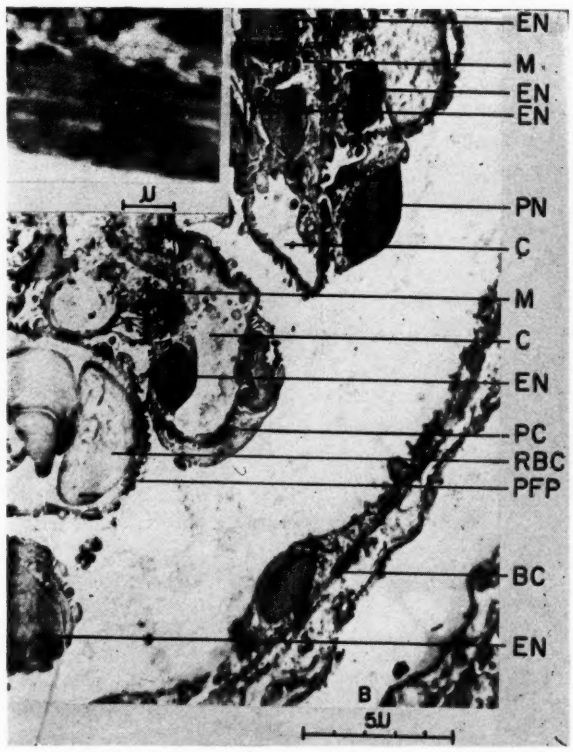


FIG. 3. The glomerulus as seen by electron microscopy. A, an oblique section through the basement membrane of Bowman's capsule (human). B, a portion of the glomerulus, the space of Bowman's capsule and Bowman's capsule with its epithelium. The space in the lower right corner is a portion of a peritubular capillary (human).

in 1877, who saw that the nuclei of adjacent cells lay side by side in eccentric positions. These cells are continuous with the epithelium of the tubule, and are also continuous with the podocytes. The major portion of the cell is thin and flat but at one point it bulges to accommodate the nucleus. The basal cell membrane is adjacent to but not a part of the basement membrane of Bowman's capsule. On the free surface of the cell there are microvilli measuring 400 Å in thickness and up to 1,800 Å in length.

Epithelium of the Glomerulus—Podocyte. The presence of epithelium overlying the capillaries, continuous with the epithelium of Bowman's capsule and of the tubule, was unequivocally denied by Bowman, who described the capillary vessels as being "so perfectly bare that in no other situation in the body do capillaries admit of being so satisfactorily studied." Gerlach[9] in 1845 and 1848 injected the tubules through the ureters and concluded that the capillaries were separated from the capsular space by cells which formed a layer over the tips and crevices of the glomerular lobules. In 1872 Ludwig[10] saw that the walls of the capillaries were separated from the capsular contents by "a layer of not very well defined cells with spherical nuclei." Gross[11] in 1919 preferred to think of this layer as a syncitium rather than true epithelium. Zimmermann[4,5] in 1929 and 1933 described these cells as pericytes while von Moellendorf[12] in 1930 called these same cells "deck zellen" and described long-branching anastomosing processes which formed a network over the glomerular loops. McGregor[13] in 1929 concluded that epithelial cells form a complete single layer

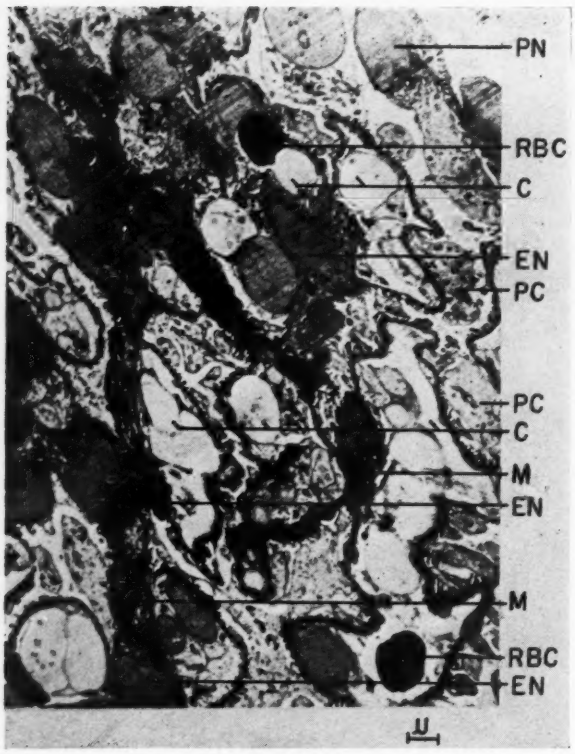


FIG. 4. Low power view of the substance of a glomerulus. This demonstrates the prevalence of podocytic material (PC) in the crevices of the glomerular lobules, and shows the relationship of the capillary lumina (C) to the endothelial glomerular stalk (M); (dog).

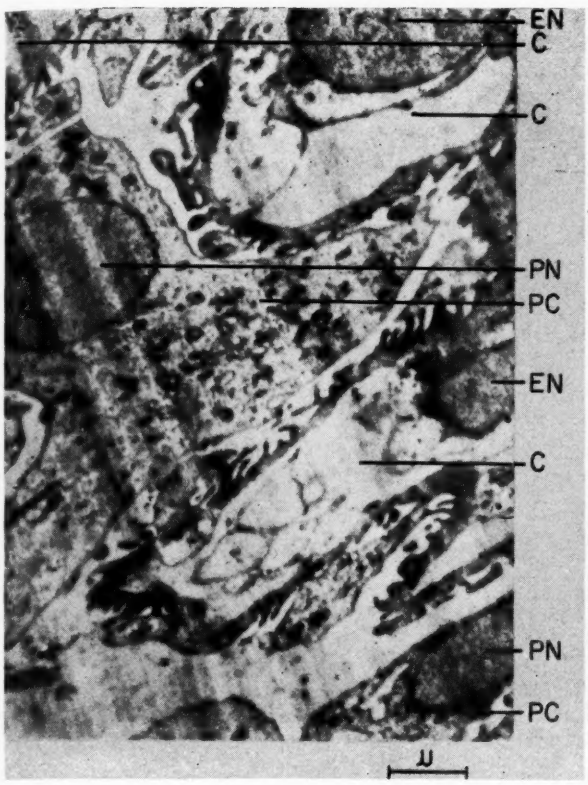
covering the tips and crevices of the capillary tufts. She stated that these cells were continuous with the capsular and tubular epithelium, that they lay outside the glomerular basement membrane, and were not syncitial.

Our studies show that the epithelial cells (podocytes) are interwoven, have large, spherical nuclei (PN) and fairly large cell bodies (PC). They are astrocyte-like in shape and possess many long protoplasmic arms (trabeculae) which extend in all directions and end in small dendriform processes (podocyte foot processes) that lie on the basement membrane. These foot processes cover the external surface of the capillaries and interdigitate with similar processes arising from other protoplasmic arms (trabeculae) from its own or other cell bodies. We believe that the podocytes represent epithelial cells of a very specialized nature. Epithelium, by definition, is a surface covering of cells whose lateral borders are in intimate apposition with those of its neighbors. By this concept the podocytes are not true epithelium. They do, however, have a position in relation to the basement membrane which compares with that of the epithelium of the tubule and Bowman's capsule. By light microscopy of the fetal glomerulus (Fig. 2B), these cells appear to be cuboidal epithelium although by electron microscopy they do not have contiguous touching borders. We believe that the podocytes are homologous with the tubular epithelium and therefore may be considered as epithelial elements of the glomerulus.

Figure 4 is a low power electron photomicrograph of a part of a glomerulus. The dark circular elements (RBC) are red blood cells which appear as structureless blots. These red cells permit easy identification of the intracapillary space (C) which in this and other micrographs contains a thin granular background, presumably due to the precipitation of plasma proteins. The capillary walls appear to be dense lines, the inner surfaces of which are fairly smooth and the outer surfaces of which are everywhere covered with the small foot processes of the podocytes, except at the point where each capillary lumen touches the dense irregular area of the glomerular stalk (M). It is thus easy to identify the capillary walls and with an isolated section to know which surface is extracapillary and which is intracapillary. In the extracapillary space the many bits of protoplasm (PC) which almost fill the extracapillary space are the trabeculae of podocytes. These vary in size and the larger pieces have the podocyte nucleus in them (PN). The relationship between each capillary and the glomerular stalk will be discussed later.

The nucleus of the podocyte (PN) (Figs. 5 to 9) has a dense granular nucleoplasm in which an eccentrically placed nucleolus is occasionally seen. The nuclear membrane is a single line, 250 Å in thickness. The cytoplasm of the podocyte (PC) has a pale granular matrix and scattered throughout the cell are granules which vary in size, being 700 to 800 Å in width and 1,900 to 4,000 Å in length. The larger of these are mitochondria. The cytoplasm also contains vacuoles (Figs. 6 to 8) of varying size and shape; the largest we have seen are about 4,500 Å in length and their wall is a membrane 150 Å in thickness. We believe these are sections through the ergastroplasmic components of the cell. Both granules and vacuoles are more prevalent in the cytoplasm near the nucleus.

The shape of the podocyte is reminiscent of the protoplasmic astrocyte, with many long trabeculae extending in every direction. These tra-



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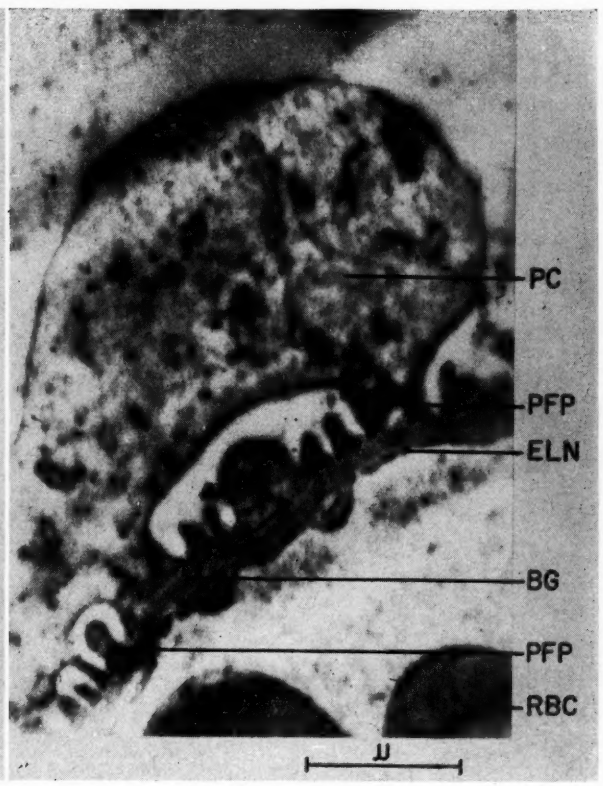

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FIG. 5. A view of a podocyte, showing its relationship to three portions of a capillary, and the congregation of mitochondria, granules and ergastoplasm in the main cell body (dog).

FIG. 6. Cross section of basement membrane of the glomerulus. Superiorly there is a trabecula showing the formation of the foot processes. Inferiorly is the capillary lumen and the inner lining network of endothelium (dog).

beculae end in foot processes which lie on the extracapillary surface of the basement membrane. The plasma membrane of the podocyte, a single layer, is 250 to 350 Å in thickness, and from pictures such as those in Figures 6 to 9 it appears that condensations of this membrane form the thick, dense foot processes.

Cross sections of these foot processes are shaped like a railroad rail. They are about 6,000 Å high and 2,200 Å in thickness. There is a clear space of about 500 Å between the capillary basement membrane and the foot process. This probably represents the maximum distance between these structures since shrinkage of tissue during fixation or following release of capillary pressure should increase this measurement. Tangential or coronal section through these foot processes (Figs. 9 to 11) reveals four or five processes some 10,000 to 12,000 Å long, projecting from a central ridge and alternately interdigitating with similar processes from a central ridge from some other, or even the same, podocyte.

In summary, then, the podocyte is homologous with the tubular and capsular epithelium. These podocytes do not form a truly continuous epithelial membrane but sit astrocyte-like over a capillary rete with many trabeculae ending in the foot processes which are applied everywhere to the extracapillary surface of the glomerular basement membrane.

The Basement Membrane of the Glomerulus. Although Bowman believed that the capsular basement membrane was not reflected over the capillary loops, most observers since then have believed otherwise. McManus[14] stated that the glomerular basement membrane is comprised of argyrophil fibers derived from both Bowman's capsule and afferent or efferent endothelium. Jones[15] held the concept that there are two basement membranes and states that "the normal glomerulus . . . consists of complex loops of capillaries having their own delicate basement membrane. An epithelial basement membrane and the covering glomerular epithelium extend around Bowman's capsule and are reflected over

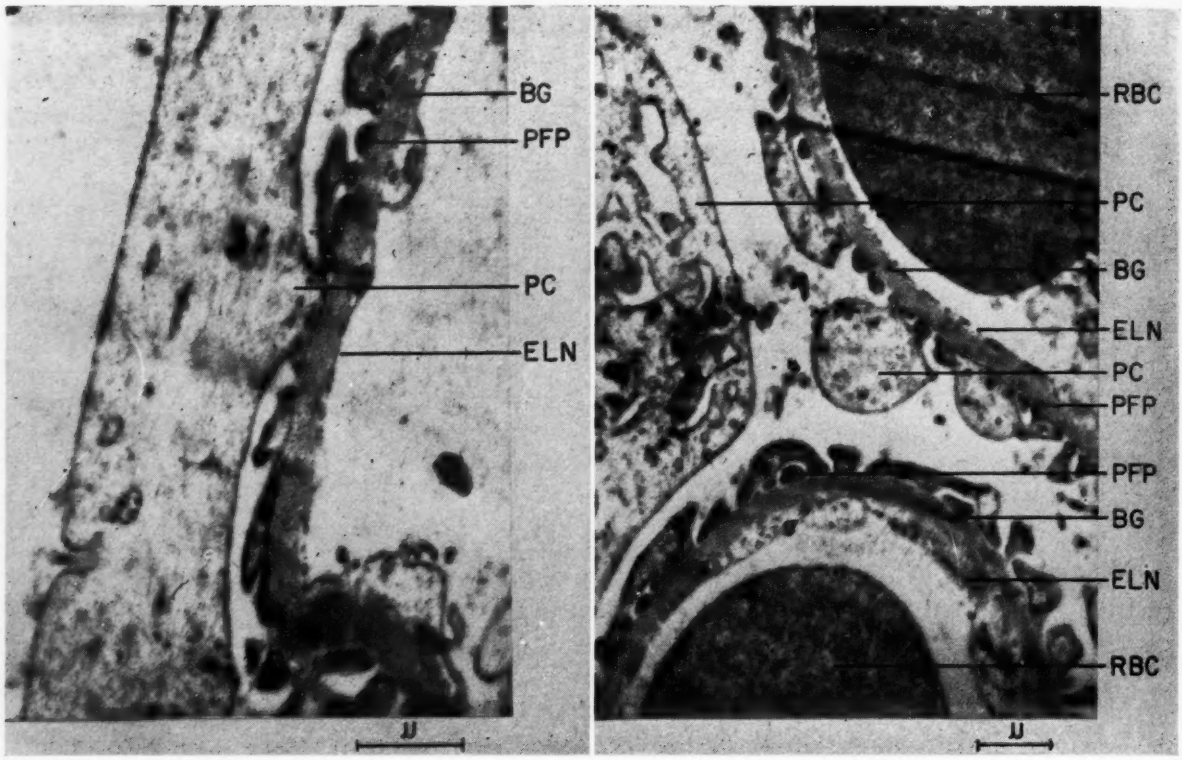

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FIG. 7. A view of the basement membrane (BG) of the glomerulus showing a trabecula of a podocyte to the left. Foot processes (PFP) are adjacent to the basement membrane. To the right of the basement membrane is a capillary lumen and endothelium (human).

FIG. 8. Sections of two portions of a capillary, with a red blood cell in the lumen of each. To the left is a portion of a podocyte with its ergastoplasmic sac distended. The endothelium in the superior capillary appears interrupted, while in the inferior capillary much of the endothelium is a continuous structure (human).

the capillary loops as the peritoneum is reflected over small bowel. Thus between an endothelial cell and an epithelial cell are an endothelial basement membrane, a pericapillary connective tissue space, and an epithelial basement membrane. In the places between capillaries, opposite layers of epithelial basement membrane almost meet but leave a small space (the so-called intercapillary space, the glomerular stalk, the mesangium)." Kimmelstiel and Wilson[16] have described hyaline deposits in the intercapillary space but did not clearly define the anatomic relationship of this space to the remainder of the glomerular elements.

We have found the basement membrane of the glomerulus (BG) to be a single homogeneous membrane 2,000 to 2,400 Å thick. We have been unable to see any structure in this membrane, and specifically no pores such as have been described by Hall.[3] The basement membrane is in close apposition to the foot processes of the podocyte on its extracapillary surface. It is in close apposition to the endothelial cell body (EC) or the expanded portion which forms the capillary wall (ELN) on its intracapillary surface. There is never an area in which basement membranes are directly "back-to-back." We have always observed a portion of an endothelial cell body lying in such a position between two basement membranes, and have never recognized collagen fibers here.

The Glomerular Capillary Endothelium. The endothelial cells of the glomerulus were observed by the early anatomists because of their projection into the capillary lumina. It is apparent from the drawings and descriptions of both Zimmerman and von Moellendorf that the nuclei of these cells, with their cell bodies, actually comprised the core about which the capillary wound into and out of the glomerulus. Goormaghtigh[17] recognized this stalk and called it mesangium. He believed that it contained fibroblasts or other mesenchymal elements. Our studies indicate that it is composed solely

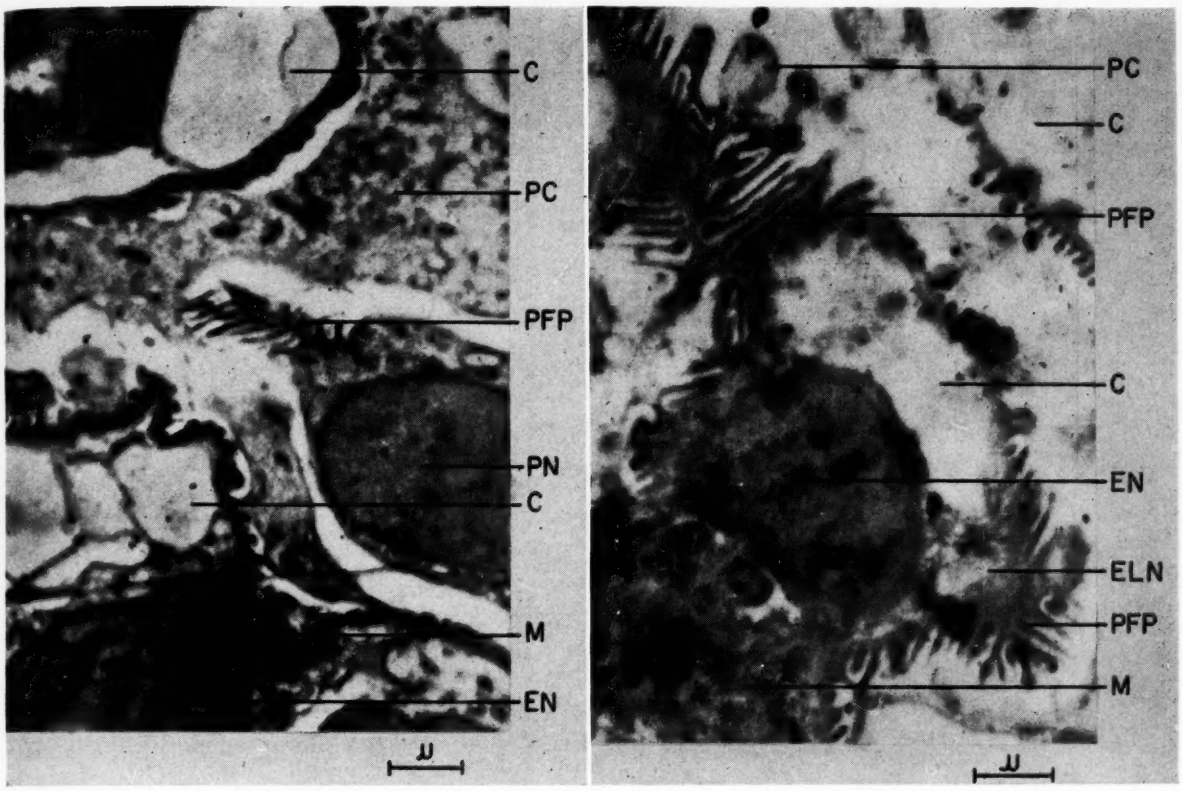

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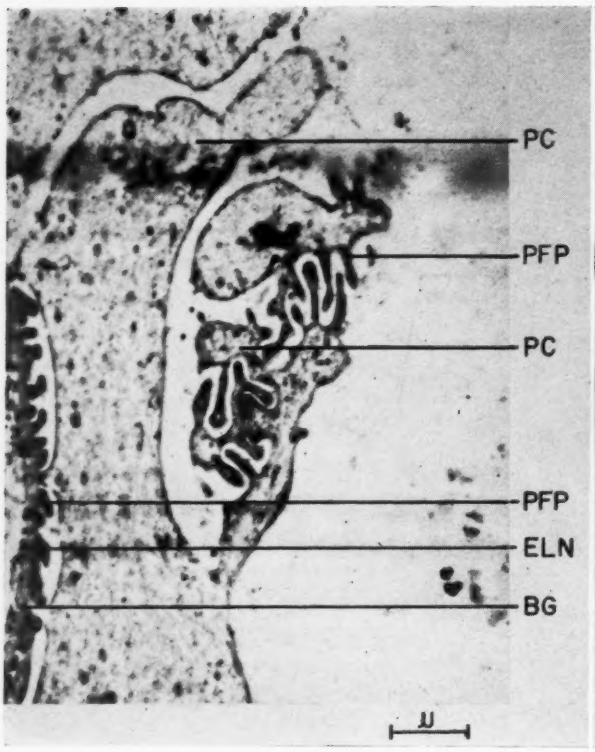
FIG. 9. A section showing the transformation of a podocyte body into a trabecula and then into arborescent foot processes which interdigitate with the foot processes from another trabecula (human).

FIG. 10. A view which shows two areas of interdigitating foot processes cut in coronal section (dog).

of the endothelial syncitium. With the electron microscope the size, shape and position of endothelial cells have been determined and the relation of endothelium to the glomerular stalk (mesangium) can be clarified. The endothelial cell (Fig. 1*f*) has three distinct parts: (1) the nucleus (EN), (2) the cell body proper (EC) which surrounds the nucleus, and (3) the inner lining network (ELN), a portion of the cell cytoplasm which is a thin, flattened protoplasmic layer, completing the capillary tube and lying adjacent to the intracapillary side of the basement membrane of the glomerulus.

The endothelial nuclei (EN) are usually ovoid in shape. (Figs. 4, 5 and 14.) The nuclear membrane is 120 Å in thickness, and the nucleoplasm is a moderately dense granular substance in which occasionally an eccentrically placed nucleolus can be seen.

The cytoplasm of the endothelial cell (EC) surrounding the nucleus is scant (Figs. 5 and 14). It is fairly clear, containing but a few granules and vacuoles. Away from the nucleus the endothelium thins out to form the capillary wall. In cross section this portion usually appears as flattened vascular endothelium with small bits of endothelial cytoplasm contained between two plasma membranes. (Figs. 6 to 8 and 14.) Often it appears as an interrupted layer with alternating thick and thin areas. The thickness of the dense area averages 550 Å. The capillary endothelium, when seen in tangential or coronal section (Figs. 12 and 13), occasionally looks like an ordinary "chicken wire" fence. Apertures in this endothelium average 650 Å in diameter (varying between 460 A and 780 Å) and the endothelium forming the apertures averages 450 Å in width. The basal cell membrane of endothelium lies 400 Å from the basement membrane, and we have not found any pedicles which connect the endothelium to the basement membrane. It is impossible to say at present whether or not the apertures in the endothelial wall are completely void of tissue, resulting in a truly fenestrated membrane, or whether there is a very thin layer of apposed plasma membranes covering this aperture. If these apertures were indeed covered by an outer and inner cell



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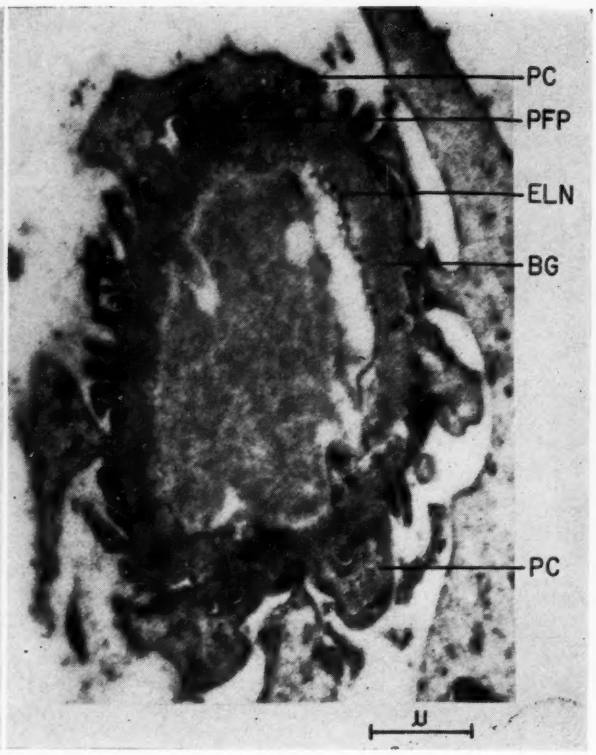

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FIG. 11. A trabecula of a podocyte showing transformation into the foot processes seen on coronal section. These foot processes interdigitate with the foot processes from another trabecula (human).

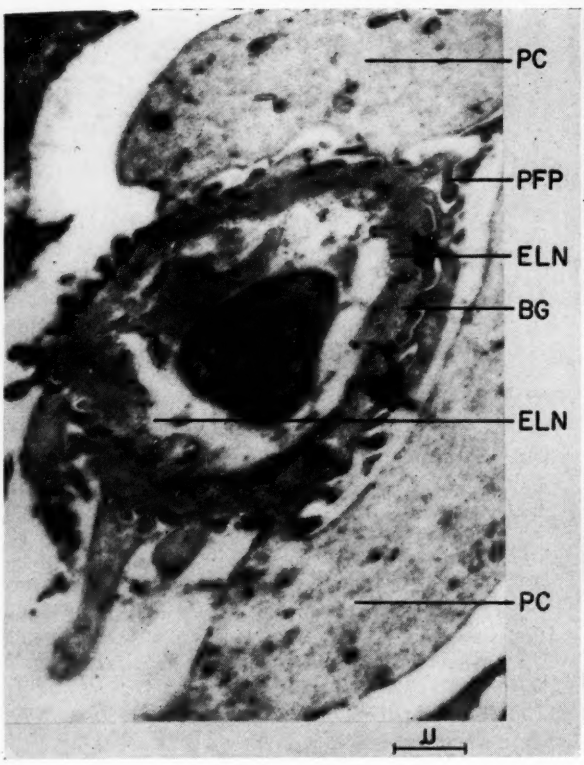
FIG. 12. Tangential section of the outer portion of a capillary, showing foot processes, basement membrane cut obliquely and *en face* appearance of the endothelial lining network (human).

membrane lying "back-to-back," such membranes ought to be visible with microscopy that resolves lines 50 to 75 Å thick. It is possible that (1) the aperture is open, (2) there is too thin a layer of membrane to be resolved, (3) in the fixation process tissue shrinkage and alteration is enough to disrupt the protoplasm filling these apertures, or (4) this appearance of the endothelium is entirely an artifact.

The portion of the endothelial cell body which is to the opposite side of the nucleus from the capillary lumen has been found to be identical with the glomerular stalk. The endothelial plasma membrane adjacent to the glomerular basement membrane cannot be traced behind the nucleus and it appears that the many endothelial cells comprising the stalk are a true syncitium.

The Supporting Stalk of the Glomerulus—the Mesangium. Since 1865, when Key[18] described some star-shaped cells in the glomerulus which he considered to be connective tissue between the glomerular loops, the presence of connective tissue in the glomerulus has been a center of controversy. With the concept that Bowman's capsule became reflected over the capillaries at the hilum, there arose the concept of an actual or potential space where two layers of the visceral basement membrane lay "back-to-back." This was likened to the arrangement in the abdomen where the parietal peritoneum forms the mesentery of the small gut, the space in this instance being filled with fat, blood vessels, lymphatics, etc. Thus in the glomerulus a mesentery for the blood vessels (mesangium) was conceived, and it is this space which is called the intercapillary space by Zimmerman, Kimmelsteil and Wilson, McManus and others. It is here that hyaline deposits are thought to occur in disease states.

In observing the glomerulus by routine light microscopy it appears that the capillaries divide at the glomerular root into four, six or eight primary branches which descend into the glomerular space and back out again without any anastomoses between the individual primary branches. Each primary branch may divide several times while in the glomerular space, reuniting with itself and returning to the hilum where it unites with other primary branches



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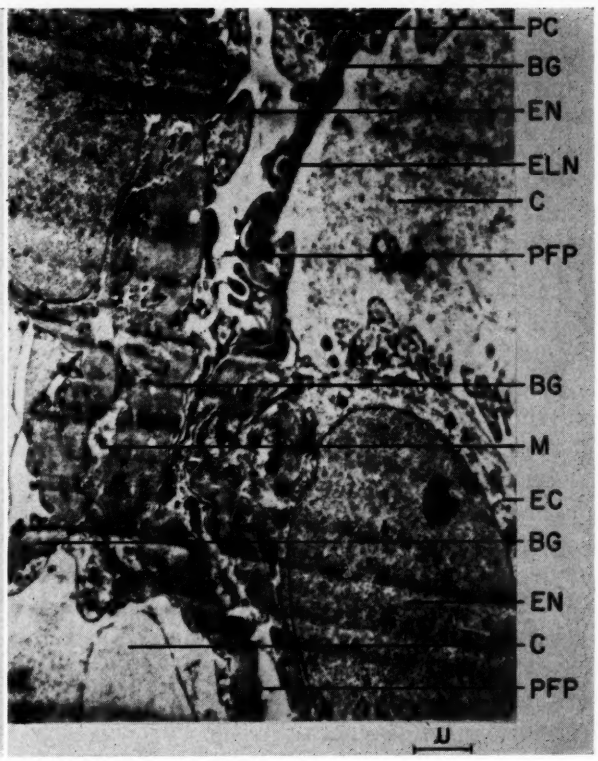

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FIG. 13. Section similar to Figure 12 (human).

FIG. 14. A view to show an area where two basement membranes come almost "back-to-back" with a small amount of endothelial cell body material (M) between them. In the upper left is an endothelial nucleus. The plasma membrane of this cell is lost in the area inferior to this nucleus (human).

to exit as the efferent arteriole.[19] In methacrylate sections cut 0.5 to 1 micron thick, stained with silver and seen with routine light microscopy, it becomes apparent that there is a central stalk or core around which the capillaries course into the glomerulus, and from which they can rarely if ever be found detached. If the capillaries should lie free in the glomerular capsule, several sections across the glomerulus should reveal cross sections or oblique sections in which the extracapillary space could be seen completely to surround the capillary. We have seen only three pictures in our material in which such a situation is present. Two of them are reproduced in Plates 12 and 13, and we feel that these represent tangential cuts across the outer portions of a capillary away from its attachment to the central core.

The position of the endothelial cell nucleus is usually at or very near to the attachment of the capillary to the glomerular stalk. (Fig. 14.) It is rare to find an endothelial cell body and its nucleus out in the periphery of a capillary opposite to the stalk, as is seen in the lower left corner of Figure 3. Even in such a situation as this it is not impossible to imagine that this cell body comprised the supporting stalk at a position above or below the plane of section. The glomerular stalk then is comprised of endothelial cell bodies between which intercellular membranes have not been demonstrated. The mesangium is actually this stalk of endothelium which extends down into the glomerulus from the hilum. The outer portions of these endothelial cells are hollowed out into the capillary space, while the central syncitium retains the nuclei. This syncitium of cells constitutes the stalk around which the capillary lumen descends into and out of the glomerulus. We have not observed the presence of collagen fibers in this stalk, nor have we seen cells which could be called fibroblasts. Future work with pathologic material may resolve the problem of the presence of connective tissue in the glomerular stalk.

The outer surface of the endothelium is invested with basement membrane continuous with that of Bowman's capsule. Its epithelial covering, cuboid in the fetus, is transformed into the interdigitating podocyte of the adult. This arrangement, as a podocyte, whereby the epithelium is lifted away from the basement

membrane permits filtration to occur without the filtrate being required to pass through the epithelial cell itself. Filtrate may thus be permitted to pass through the endothelium, through the basement membrane and then between the podocyte foot processes and under the trabeculae of the podocytes to arrive in the free space of Bowman's capsule.

CONCLUSIONS

The basement membrane of the renal tubule is expanded over the glomerulus as Bowman's capsule and is then reflected onto the capillary endothelium as a continuous structure. There is only one basement membrane in the glomerulus.

The epithelium of the renal tubule is continuous with that of the epithelium of Bowman's capsule and is homologous with the podocytes.

The glomerular epithelium is composed of an interdigitating group of cells—podocytes—which lie over and between the loops of a capillary. These cells are shaped like astrocytes. They have long, thick trabeculae which end in slender dense foot processes that lie on the extracapillary surface of the glomerular basement membrane to interdigitate with the foot processes from other trabeculae of the same or other podocytes.

The glomerular endothelium through which filtration must occur is a thin layer of protoplasm, occasionally having a "chicken wire" appearance. This lies just inside the basement membrane of the glomerulus.

The cell bodies of the glomerular endothelium are syncitial and form a stalk around which the capillary rete courses into and out of the glomerulus. This endothelial stalk constitutes what has been called the intercapillary space—the glomerular stalk, or the mesangium. It is composed of endothelial cells whose adjacent boundaries cannot be defined.

There is no difference between dog and man in the structures contained in the glomerulus, in the size of these structures, or in the arrangement of these structures into the glomerular unit.

Acknowledgment: We are indebted to Dr. Edward Dempsey and all members of the Department of Anatomy for helpful advice regarding the preparation of tissues, the use of the electron microscope and the interpretation of the electron micrographs.

REFERENCES

1. Dempsey, E. W. and Lansing, A. I. Improved knife holders for thin-sectioning with rotary microtomes. *Proc. Soc. Exper. Biol. & Med.*, 82: 253–256, 1953.
2. Wilder, H. C. An improved technique for silver impregnation of reticulum fibers. *Am. J. Path.*, 11: 817–819, 1935.
3. Hall, B. V. Proc. Fifth Annual Conference on the Nephrotic Syndrome, 1953.
4. Zimmermann, K. W. Über den Bau des Glomerulus der menschlichen Niere. *Ztschr. f. mik-anat. Forsch.*, 18: 520–552, 1929.
5. Zimmerman, K. W. Über den Bau des Glomerulus der Säugerniere. *Ztschr. f. mik-anat. Forsch.*, 32: 176–278, 1933.
6. Bowman, W. On the structure and use of the malpighian bodies of the kidney with observations on the circulation through the gland. Reprinted in *Med. Classics*, 5: 249–291, 1940–41.
7. Seng, V. Ein Beitrag zur Lehre von den Malpighi'schen Körperschen der menschlichen Niere. *Sitzungsb. d. k. Akad. d. Wissensch.*, 64: 354–358, 1871.
8. Drasch, O. Über das Vorkommen zweierlei verschiedner Gefässknaul in der Niere. *Sitzungsb. d. k. Akad. d. Wissensch.*, 76: 79–102, 1877.
9. Gerlach, J. Zur Anatomie der Niere. *Arch. f. Anat., Physiol. u. wissensch. Med.*, pp. 102–112, 1848.
10. Ludwig, C. Manual of Human and Comparative Histology. *The New Sydenham Soc., London*, 2: 83–106, 1872.
11. Gross, W. Frische Glomerulonephritis. *Beitr. z. path. Anat. u. z. allg. Path.*, 65: 387–422, 1919.
12. von Moellendorf, W. Der Exkretionsapparat. *Handbuch der mikro. Anat.*, 7: 1–328, 1930.
13. McGregor, I. The finer histology of the normal glomerulus. *Am. J. Path.*, 5: 545–558, 1929.
14. McManus, J. F. A. Medical Diseases of the Kidney. Philadelphia, 1950. Lea and Febiger.
15. Jones, D. B. Glomerulonephritis. *Am. J. Path.*, 29: 33–52, 1953,
16. Kimmelstiel, P. and Wilson, C. Intercapillary lesions in the glomeruli of the kidney. *Am. J. Path.*, 12: 83–106, 1936.
17. Goormaghtigh, N. The renal arteriolar change in the crush syndrome. *Am. J. Path.*, 23: 513–529, 1947.
18. Key, E. A. On circulations for hallendena i. Njurarne. *Forh v. de skandin. Ñaturf., Stockholm*, pp. 685–725, 1865.
19. Hall, B. V. Salisbury Cove Symposium 1954, unpublished.
20. McManus, S. F. A. The structure of the glomerulus. *Am. J. Path.*, 24: 1259–1265, 1948.
21. Dalton, A. J., Kakler, H., Streelich, M. J. and Lloyd, B. Structural details of some of the epithelial cell types in the mouse as revealed by the electron microscope. *J. Nat. Cancer Inst.*, 11: 1163–1185, 1951.
22. Rinehart, J. F., Farquhar, A. B., Jung, H. C. and Abul-Haj, S. K. The normal glomerulus and its basic reactions in disease. *Am. J. Path.*, 29: 21–32, 1953.
23. Pease, D. C. and Baker, R. F. Electron microscopy of the kidney. *Am. J. Anat.*, 87: 349–390, 1950.
24. Reid, R. T. W. Observations on the structure of the renal glomerulus of the mouse revealed by the electron microscope. *Australian J. Exper. Biol. & M. Sc.*, 32: 235–240, 1954.

The Clinicopathologic Meaning of the Nephrotic Syndrome*

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IT is apparent from the current literature that there still prevail fundamental differences of opinion concerning the existence, nature and physiologic meaning of the renal lesions responsible for or, preferably, associated with the clinical syndrome commonly known as "lipid nephrosis." Moreover there are some observers, a minority of them, who altogether dissociate the kidney from any primary or significant role in the initiation and development of this disorder. The range of primary pathogenetic concepts that have been and for the most part continue to be advocated includes (1) an excess of antidiuretic hormones; (2) the presence of abnormal proteins ("dysproteinemia") to which the kidneys are especially permeable; (3) a derangement of cholesterol metabolism, perhaps related to thyroid dysfunction; (4) the mechanism implied in the vague but popular cliché "glomerulotubular imbalance," referring to either "glomerular insufficiency" or "tubular preponderance"; and (5) an abnormal glomerular permeability with or without histologically demonstrable glomerular lesions, and also abetting "glomerulotubular imbalance." As a corollary of this last concept, the point of view persists—a recent attempt to dislodge it having apparently been unimpressively effective[1]—that "chronic (lipid) nephrosis" is an entity quite separate clinically, morphologically and etiologically from the nephrotic stage of chronic glomerulonephritis (e.g., Ellis,[2] Ehrich,[3] Fishberg[4]). This same hypothesis is embodied in Ellis's classification of "type I" and "type II" nephritis, "type II" representing lipid nephrosis of insidious onset and of an etiology, course and histology different from the overt, usually postinfectious "type I" glomerulonephritis in which hematuria, azotemia and hypertension appear.

The precise site of renal dysfunction, if one is present, does not seem to have been demonstrated with credible constancy by the use of clearance or morphologic studies. The wide variability of the data derived from the clearance studies has naturally led to conflicting interpretations of their meaning in terms of renal dysfunction and especially in terms of renal organic changes. What perhaps needs to be done is not to disregard or minimize the significance of this variability by attributing it to the limitations of the investigative method, a matter that can be settled statistically, but rather to determine if there are adequate morphologic explanations available for these disparate physiologic data. It is with this phase of the problem, as well as with the clarification of the relationship of "lipid nephrosis" to glomerular and tubular lesions, that this paper is principally concerned.

DEFINITION

It is universally agreed that the clinical syndrome of lipid nephrosis consists of (1) proteinuria, principally albuminuria; (2) hypoproteinemia; (3) hypercholesterolemia; (4) lipiduria with "oval fat bodies" and bifringent lipid masses and crystals; and (5) edema in the form of anasarca and effusions. Morphologically, in all instances of the nephrotic syndrome the kidneys are large or, at least unshrunken, the convex surfaces relatively smooth, the cortex swollen and yellowish, and the proximal tubular epithelium vacuolated with lipid, some of which is anisotropic, and occasionally filled with hyaline droplets. This clinical complex is often referred to as the "pure" syndrome, which hereinafter will be indicated by the terms "lipid nephrosis" or "nephrotic syndrome." It is distinguished from the "impure," "mixed" or "complicated" lipid nephrosis in which hematuria, hypertension, varying amounts of pyuria, and azotemia

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may be added. Elevation of the serum levels of alpha (particularly $alpha_2$) and beta proteins and depression of gamma globulin is characteristic of some forms of the nephrotic syndrome but not of others; it is characteristic of diffuse membranous glomerulonephritis but not of diabetic glomerulosclerosis in which the concentration of gamma globulin is usually normal or slightly elevated, nor of the nephrotic syndrome due to disseminated lupus erythematosus in which the level of gamma globulin is also elevated, as a rule.

The foregoing syndrome of lipid nephrosis, "pure" or "complicated," occurs in each of several disorders notwithstanding the diversity of the pathologic changes. Secondary physiologic, immunologic and clinical variations occur, depending on such factors principally as duration, nature and severity of the renal lesions, superimposed immunologic reactions, integrity of the liver, and nutritional status of the patient. These entities are morphologically classified as follows: (1) diabetic glomerulosclerosis; (2) glomerular amyloidosis; (3) membranous or lobular glomerulonephritis (including that due to syphilis, the typhus fevers, chiefly the quartan variety of malaria, and many other infections as well as the nephritis associated with toxemias of pregnancy, poison oak dermatitis, x-radiation and the use of drugs (e.g., cortisone, nitrogen mustards, triethylene melamine (TEM), 6-mercaptopurine (6-MP) etc.);[1,5–11] and (4) bilateral renal vein thrombosis.*[1,4,12]

Our thesis is that in all instances of lipid nephrosis, "pure" or "mixed,"—with one possible exception—there is a diffuse, organic, histologically demonstrable lesion of the glomeruli. The one possible exception may be the extremely rare instance of lipid nephrosis secondary to bilateral renal vein thrombosis. However, even if no organic lesions have been demonstrated in the limited material available, it appears clear that the basis for the proteinuria —and hence the nephrotic syndrome—in bilateral renal vein thrombosis is the increased pressure within the glomerular capillaries produced by the elevated pressure in the venous system behind the thrombosed veins and resulting in abnormal permeability to proteins. In each of the other three categories the glomerular lesions have an individual microscopic pattern which not only is fairly readily recognizable but which also may be correlated with most of the important aspects of the altered physiology. The morphologic details of each of the lesions in these separate categories, along with an analysis of their physiologic meaning, will be briefly outlined in the following sections.

* The evidence is unconvincing that chronic pyelonephritis ever causes the nephrotic syndrome although rare questionable reports to the contrary are found.

DIABETIC GLOMERULOSCLEROSIS

In about one-third of the patients over forty years of age with diabetes mellitus, a characteristic form of focal glomerulosclerosis occurs which, with few exceptions, is readily identifiable even in sections routinely stained with hematoxylin and eosin.[13] This lesion, originally termed "intercapillary glomerulosclerosis" in the pioneering article by Kimmelstiel and Wilson,[14] appeared, on the basis of studies of serial sections,[15] to be made up actually of a segmental, spherical sclerosis of the glomerular capillaries. (Fig. 1.) It was therefore referred to first as "intramural glomerulosclerosis" and subsequently as "diabetic glomerulosclerosis";[1,15] the latter designation seems to have become more acceptable. That the lesion is in fact a form of capillary sclerosis, rather than a focal thickening of the hypothetical mesangium or fibrous tissue that is presumed to exist between glomerular capillaries, is a conclusion about which the author, at least, has no reasonable doubt. This conclusion, which has been confirmed by Bell,[9] has recently received strong support from the informative electron microscopic studies of Hall.[16] This histogenesis of diabetic glomeruloscerlosis is not a matter of tedious morphologic nicety; it is clearly of considerable physiologic and pathogenetic significance whether or not a lesion is truly vascular or involves merely the supporting stroma between vessels. The detailed evidence for the histogenesis has been set down elsewhere and will not be repeated here.[1,15]

At any rate it is now generally agreed that the lesion for all practical purposes is pathognomonic of diabetes mellitus. When widely distributed, these lesions are associated with the nephrotic syndrome, usually of the "mixed" type, with hypertension, slight hematuria and renal insufficiency of varying degree.[13] As stated, there is less tendency for the gamma globulins to be depressed in diabetic glomerulosclerosis than in membranous glomerulonephritis although the $alpha_1$ and $alpha_2$ globulins are usually elevated

appreciably, and the beta globulins slightly, if at all.[16a]

Of immediate relevance to this paper is the mechanism by which the nephrotic syndrome is brought about in diabetic glomerulosclerosis. In compliance with the thesis that excessive glomerular permeability to proteins is the critical factor in the nephrotic syndrome, it is suggested that diabetic glomerulosclerosis in some manner alters this permeability. It does not seem reasonable that the argyrophilic, trypsin-resistant, dense, hyaline masses constituting the major element of diabetic glomerulosclerosis are the source of the increased permeability. However, as has been previously pointed out,[15] it is evident from serial sections of the diabetic lesions that a capillary loop is enormously dilated and stretched around practically each of the hyaline spheres, as if the dilatation were the result of capillary stenosis produced by the spheres encroaching on the capillary lumens. Because of the long accepted fact that even moderate dilatation of capillaries results in their becoming abnormally porous to proteins, it was theorized that these markedly dilated glomerular capillaries that loosely envelope the hyaline bodies of diabetic glomerulosclerosis might well be the mechanism responsible for the loss of protein in the urine about which the nephrotic syndrome revolves. (Figs. 1 and 3.) Moreover, there is reason to suggest that the dilatation of glomerular capillaries may result in greater permeability than equal dilatation of capillaries of other structures or organs. For example, Pappenheimer[17] states that "the flow (of fluid) through glomerular capillary membranes occurs one hundred times more readily than through capillary walls in muscle and serves to emphasize the fact that capillary walls in different tissues may offer widely varying resistances to the flow of fluid through them." It was also noted that the walls of the usually overlooked efferent arterioles of kidneys with diabetic glomerulosclerosis were commonly thickened and their lumens narrowed (as were those of the afferent arterioles), thereby presumably causing an increased intraglomerular pressure which might conceivably add an extra increment to the proteinuria.[15] In addition, inasmuch as it is assumed that angiotonin (hypertensin) produces experimental hypertension by causing constriction of efferent arterioles with a consequent rise of intraglomerular pressure,[18] it was suggested that efferent arterioles that were already organically narrowed might exert a parallel effect and thereby help to account for the greater incidence of hypertension among diabetics over forty years of age than in a corresponding age group of non-diabetics.[15] It is possible, too, that the diabetic glomerulosclerosis itself, through narrowing of the intraglomerular capillaries, may also contribute to the hypertension in a fundamentally similar manner. These are the principal morphologic features, it is believed, which account for the main clinical components caused by diabetic glomerulosclerosis.

The pathogenesis of diabetic glomerulosclerosis is still imperfectly understood. The recently proposed hypothesis that the lesions are provoked by the local deposition of lipid is untenable for several reasons, chief among which is its failure to account for the absence of these lesions among patients with lipid nephrosis due to membranous glomerulonephritis; the glomeruli of these latter patients often contain abundant lipid. (Figs. 13 and 20.) Of greater interest is the production, in "anaphylactically sensitized" rabbits treated with cortisone, of glomerular lesions described as "indistinguishable" from those of diabetic glomerulosclerosis.[19] This experimentally produced lesion is pictured in Figure 23. However, in this reviewer's opinion the remarkable alteration represents a focal, partly sudanophilic, fibrinoid degeneration of the walls of the glomerular capillaries, corresponding more closely to the change of disseminated lupus erythematosus or to focal necrotizing allergic glomerulitis than to the laminated, argyrophilic, trypsin-resistant sclerosis of the diabetic lesion which, as mentioned, characteristically is enveloped by dilated thin-walled capillaries. (Figs. 2 and 3.) Nor does it seem likely that this experimental lesion might be equivalent to an "acute" stage of diabetic glomerulosclerosis. In other words the lesion caused by cortisone appears to represent an acute focal membranous glomerulitis. It is relevant, in this regard, to cite the case in which a diffuse membranous glomerulonephritis in a patient with periarteritis nodosa was attributed to the administration of cortisone.[11] As matters stand the pathogenesis of diabetic glomerulosclerosis must be considered unresolved although the most acceptable likelihood is that the process constitutes a form of capillary sclerosis which, with a peculiar specificity, localizes to the glomeruli of diabetics.

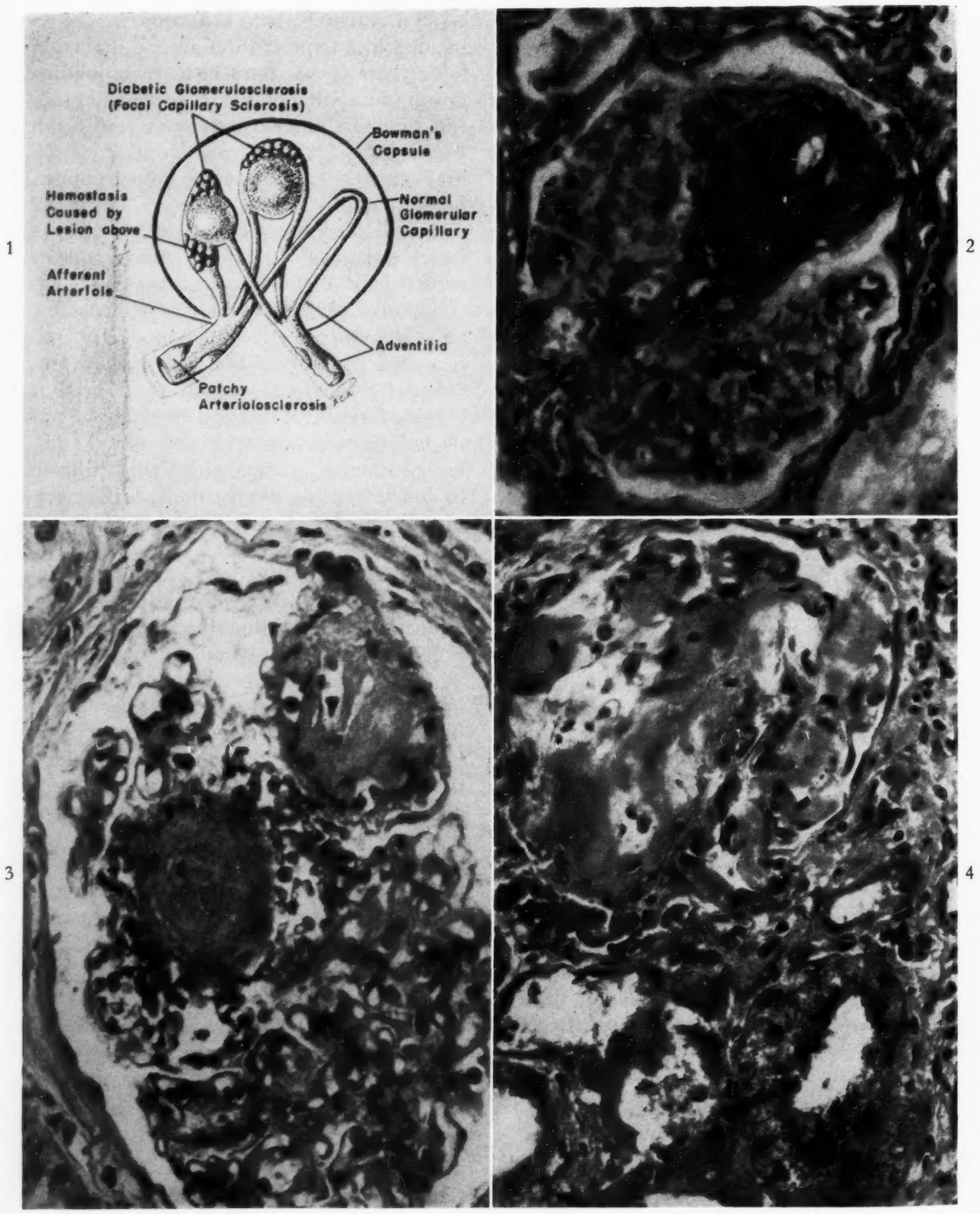

FIG. 1. Diagrammatic representation of the capillary (vs. intercapillary) origin of diabetic glomerulosclerosis.

FIG. 2. Laminated argyrophilia of diabetic glomerulosclerosis; (modified Bielschowsky's stain, × 210).

FIG. 3. Aneurysmal dilatation of a thin-walled glomerular capillary about a lesion of diabetic glomerulosclerosis; (hematoxylin and eosin, × 280).

FIG. 4. Glomerular amyloidosis with hyaline droplets in the epithelium of the proximal convoluted tubules; (hematoxylin and eosin, × 280).

GLOMERULAR AMYLOIDOSIS

The mechanism of the proteinuria and the nephrotic syndrome is essentially similar in glomerular amyloidosis and in diabetic glomerulosclerosis. As a matter of fact the hyaline spheres of diabetic glomerulosclerosis superficially resemble those of amyloidosis when viewed with routine stains; the tinctorial and structural differences have been previously described.[1] (Fig. 4.) Here again the tubular changes—the lipid, hyaline droplets, proteid casts—are often so prominent that, even currently, renal amyloidosis with the nephrotic syndrome is referred to as "amyloid nephrosis" and in most textbooks is included in the sections dealing with diseases of renal tubules. It may be taken as a rule, without exception so far as this author is aware, that the nephrotic syndrome does not occur in renal amyloidosis without *glomerular* amyloidosis and, more than that, without *extensive* glomerular amyloidosis. It is entirely possible that the increased glomerular permeability in amyloidosis is caused not only by the dilated capillaries about the hyaline masses but also, as in membranous glomerulonephritis, by an abnormal permeability of glomerular capillaries which have been only slightly but diffusely thickened by the possibly abnormally porous amyloid. (Fig. 4.) Contrariwise, the diffuse, firmer or denser thickening of the walls of glomerular capillaries in benign nephrosclerosis or the thickening that may accompany or antedate the development of focal diabetic glomerulosclerosis does not seem to affect glomerular permeability significantly. With contraction of the amyloidotic kidney (Fig. 30) there is a tendency toward regression of the signs and symptoms of the nephrotic syndrome as well as toward the development of hypertension and azotemia. This aspect of the phenomenon of renal sclerosis is dealt with further under "membranous glomerulonephritis."

As with diabetic glomerulosclerosis, there are also differences of opinion regarding the histogenesis of glomerular amyloidosis. Some[9] believe that the amyloid is deposited on the inner, luminal side of the walls of the glomerular capillaries; many others insist that the controversial intercapillary mesangium and space are the sites of amyloid accumulation. It is this author's view[1] not only that a "deposition" of amyloid material, analogous to the deposition of fat or fibrin from the blood stream, does not occur but also that the change recognized as glomerular amyloidosis represents an intrinsic alteration within the reticulin and collagen of the walls of the capillaries rather than an extramural accretion.

MEMBRANOUS GLOMERULONEPHRITIS

As previously suggested, the one site of central importance on which are dependent many physiologic and morphologic alterations is the basement membrane or wall of the glomerular capillaries.* The designation "membranous glomerulonephritis" refers to only one—by far the most common one—of the several kinds of glomerular lesions listed earlier that are responsible for the initiation and perpetuation of the nephrotic syndrome. In the author's opinion this is the basic lesion (or the morphogenetically related "lobular glomerulonephritis") that is present in all instances (exclusive of diabetic glomerulosclerosis, glomerular amyloidosis and renal vein thrombosis) to which the terms glomerulonephritis with edema, pure or mixed lipid nephrosis, genuine nephrosis, Addis' degenerative stage of glomerulonephritis,[20] and others have been applied. Membranous glomerulonephritis is also the type of lesion that may be produced, as has been personally observed in the material at the Memorial Cancer Center and elsewhere, with cortisone,[11] x-radiation,[21] nitrogen mustard, triethylene melamine, 6-mercaptopurine, penicillin, and probably gold salts,[22] tridione[23] and other drugs not yet documented, as well as certain physiologic states such as "febrile albuminuria." (Figs. 14 to 17.) This same type of change, as indicated, may occur in eclampsia (Fig. 18), the secondary stage of syphilis, relapsing fever, malaria and in association with other infections. An essentially related but microscopically distinguishable change is found, too, in disseminated lupus erythematosus

* The issue of whether or not the wall of the glomerular capillaries consists of one or two basement membranes will not be further discussed here except for this brief statement. Surely the facts of the embryologic development of the glomerulus clearly establish at least the theoretic existence of two such membranes: an endothelial one and one subtending the visceral epithelium. However, for all practical purposes these fuse inseparably and become a single membrane or wall, as has been emphasized.[1] Hence the suggestion that these membranes may suddenly be cleaved to form spaces or pockets of inflammation in acute glomerular reactions appears without foundation. Confirmation of this viewpoint has been recently supplied by the electron-microscopic studies of Hall.[16]

and, indeed, the nephrotic syndrome is for this reason common in this disease. (Fig. 19.)

Worthy of emphasis is the observation that acute diffuse membranous glomerulonephritis is not the rare lesion that many believe it to be, but, on the contrary, when proper criteria are used, may be found frequently in autopsy material from patients whose major disease overshadowed the renal disorder. Often these patients with acute membranous glomerulonephritis incidental to their principal illness (in our cases usually neoplastic disease) do not manifest the complete clinical picture of the nephrotic syndrome either because the renal disease is mild or frequently because it is part of the terminal stages of their only indirectly related illness, just as degenerative verrucal endocardiosis may be incidental to a large variety of illnesses.[24] The same type of acute membranous glomerulonephritis, it may inferentially be concluded from autopsy material, occurs also as a subordinate manifestation of other diseases which are survived, especially infectious diseases. In these latter instances the acute membranous glomerulonephritis may be assumed to regress in a high percentage of cases, again just as verrucal endocardiosis, as a general rule, becomes healed if the patient survives the primary illness.

Histology of Membranous Glomerulonephritis. The histologic essence of diffuse membranous glomerulonephritis, both acute and chronic, is an acidophilic thickening of the walls of the glomerular capillaries of the entire malpighian tuft of all the glomeruli or, at least, all of the glomeruli that are included in standard histologic sections. (Figs. 11 to 18.) The acute stage differs from the chronic in that the acute lesions tend to be less acidophilic, more granular and vacuolated, sudanophilic and softer or more porous looking than those of the chronic stage. As a rule there is no distortion of glomerular architecture in either stage although in the more fulminant acute lesions the thickening of the walls of the glomerular capillaries is less uniform than the chronic changes, the irregularities occasionally taking the form of nodular fibrinoid swellings of the capillaries. (Fig. 14.) Similar fibrinoid change may occur in Bowman's capsules and in the afferent arterioles. The acidophilic cytoplasm of swollen endothelial and epithelial cells may simulate swelling of the basement membrane on which they lie, especially in inadequately fixed and dehydrated sections. Somewhat paradoxically, despite the increased thickness of their walls these capillaries are abnormally permeable, particularly to molecules up to the size of albumin and often even to molecules as large as the globulins. Occasionally, the permeability to protein may be indicated by the presence of large amounts of granular precipitate which fill and dilate Bowman's spaces. (Fig. 11.) However, more commonly both Bowman's spaces as well as the lumens of the proximal convoluted tubules are free of protein precipitate even though there had been abundant proteinuria in the days immediately prior to death. Hence the absence of such precipitate does not indicate the integrity of the glomeruli. Proteid casts are frequently present particularly in the collecting tubules, and, occasionally, birefringent yellowish green crystals are also observed in the distal nephrons. These crystals resemble sulfonamides, oxalates or the leucine-like crystals found in association with hepatic lesions;[1] some observers regard them as of protein composition. At one time the proteinuria of lipid nephrosis was attributed to the presence of abnormal plasma proteins (dysproteinemia) against which normal glomeruli were an ineffective barrier. However, it is now generally conceded that the urinary proteins in lipid nephrosis—usually 65 to 90 per cent of which is albumin—reflect qualitatively normal blood proteins. Obversely, the Bence-Jones dysproteinuria of myeloma is not a cause of the nephrotic syndrome. Discussion of the lipid and the hyaline droplets of the tubular epithelium is reserved for a later section.

Requirement of Special Stains. Although in his studies of glomerular lesions the author has used to good advantage tryptic digestion[15] as well as a variety of special stains including the PAS, the several trichrome, modified Bielschowsky and the Gram stains, membranous glomerulonephritis is recognizable in sections stained routinely with hematoxylin and eosin and does not require any more elaborate technic for its identification. This declaration is made with full realization of the directly contrary opinions of many competent workers, but perhaps the photomicrographs of hematoxylin and eosin stained sections, published herewith and elsewhere,[1] give it some support. It need not be added that these special stains are of obvious value when appropriately applied, but the viewpoint that many types of glomerular lesions are not diagnosable without them is

inaccurate and, accordingly, somewhat of a disservice to the extent that it discourages analysis of routinely stained glomeruli and, by inference, tends unjustifiably to discredit studies of the past and present in which such special stains may not have been used or, if used, were not found contributory.

Chronic Lobular Glomerulonephritis. The term "chronic lobular glomerulonephritis" has been applied to a specific histologic lesion which is almost always associated with the clinical picture of "mixed" lipid nephrosis; that is, the nephrotic syndrome complicated particularly with hypertension and often with renal insufficiency and some degree of hematuria and pyuria.[1,25] Microscopically, as with diffuse membranous glumerulonephritis, no normal glomeruli are found. The malpighian tufts are transformed into about four or five brightly acidophilic, PAS-positive lobules which resemble the lesions of diabetic glomerulosclerosis especially since many of the lobules are loosely surrounded by dilated capillaries. (Fig. 27.) The confusion of these two lesions has been largely responsible for the few reports of the occurrence of "diabetic glomerulosclerosis" in appreciable numbers of non-diabetic patients. There are distinct differences. The lesions of lobular glomerulonephritis, as stated, spare no glomeruli, the lobules are always multiple within a single tuft, they tend to be of approximately uniform size and relatively cellular, and the walls of the surrounding capillaries are likely to be thickened or frayed. In contrast, the lobules of diabetic glomerulosclerosis may involve one, several or all glomeruli examined; they are irregular in diameter, they are generally less cellular, the enveloping capillaries are thin-walled and commonly dilated to aneurysmal proportions, and frequently only a single lesion or lobule is present and, characteristically, the single or probably initial, lobule is located opposite the glomerular hilum. (Figs. 1 to 3.) In addition, under close examination of even routinely stained (hematoxylin and eosin) sections, delicate laminations can be detected within the lobules of diabetic glomerulosclerosis. With silver stains these laminations are found to be strikingly argyrophilic (Fig. 2) whereas silver stains of the lesions of lobular glomerulonephritis reveal them to be composed of haphazardly arranged curleycues of silver fibers.[1] Sclerosis of vessels, particularly the afferent arterioles, atrophy of tubules with replacement fibrosis, and lipid, some birefringent, within the cells of the proximal convoluted tubules are the usual accompanying changes.

It is not a simple matter to deduce with certainty the histogenesis of chronic lobular glomerulonephritis. The process has been referred to by others as "simplification" of the glomerular structure but there is reason to suggest that the appearance of simplification really camouflages complex histologic changes. From the study of various stages of membranous, lobular and sclerosing glomerulonephritis the impression is gained that lobular glomerulonephritis represents a more fulminant variant of membranous glomerulonephritis in which the walls of many of the glomerular capillaries have undergone marked fibrinoid swelling and even coalescence, and in which exudative and proliferative glomerulonephritis have often been superimposed. (Figs. 32 to 34). Sclerosis with ensuing contraction of the kidneys and corresponding modification of the clinical picture may follow lobular glomerulonephritis just as it may membranous glomerulonephritis. (Figs. 31 to 35.)

Membranous and Lobular versus Other Forms of Glomerulonephritis. If membranous and lobular glomerulonephritis lead to the nephrotic syndrome, it must logically follow, if a clinicopathologic correlation does in fact exist, that the lesions of the so-called "type 1," acute hemorrhagic glomerulonephritis, in which hematuria, pyuria, azotemia and hypertension occur without the nephrotic syndrome, are distinguishable from those of membranous and lobular glomerulonephritis. Such differences do exist and they are both qualitative and quantitative, as illustrated in Figures 5 to 10. As these photographs show, the acute glomerulonephritis unassociated with the nephrotic syndrome may take any of the following morphologic forms: (1) acute exudative, (2) acute proliferative, (3) acute necrotizing, or (4) any combination of the previous three. Exudative or proliferative glomerulonephritis commonly develops without morphologically detectable or physiologically significant changes in the glomerular basement membranes. In other words, such lesions, as can be easily visualized, are organically completely reversible and, accordingly, comprise the vast number of instances of acute hemorrhagic glomerulonephritis ("type 1") that are healed after the initial attack. A small minority of cases of exudative or proliferative glomerulonephritis

is accompanied by the changes of membranous glomerulonephritis. (Fig. 32.) In these the clinical picture of "mixed" lipid nephrosis appears and, since the morphologic alterations are greater than those of membranous glomerulonephritis, the prognosis is understandably

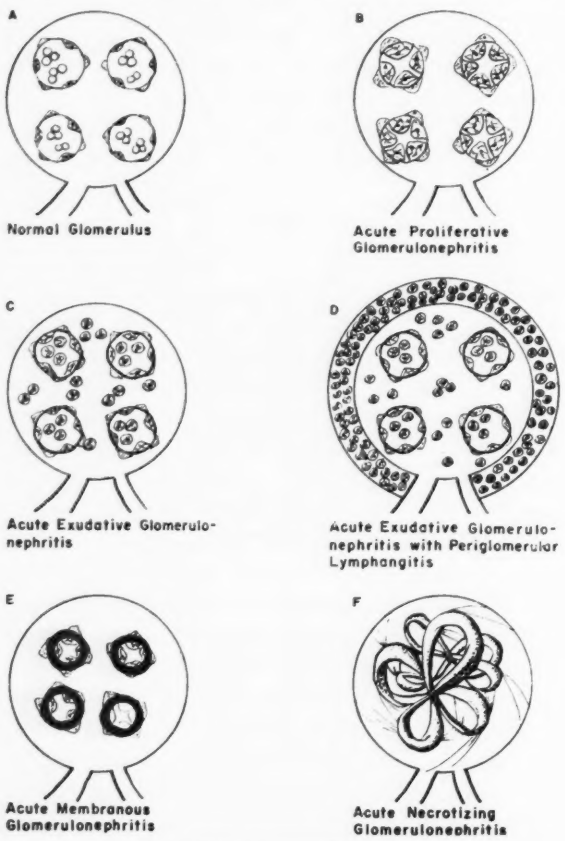

FIG. 5. Diagrammatic representation of various morphologic types of acute glomerulonephritis. (From: ALLEN, A. C. The Kidney; Medical and Surgical Diseases. New York, 1951. Grune & Stratton, Inc.)

worsened. It is of concern that a relatively high percentage of cases of membranous and lobular glomerulonephritis in adults, is associated with exudative or proliferative glomerulonephritis so that the "pure" nephrotic syndrome in adults is, for this reason, less common than the "mixed" and accordingly the outlook in these patients is correspondingly poor.

Evolution of Membranous and Lobular Glomerulonephritis. In the days prior to antibiotic therapy about 33 per cent of patients with chronic membranous or lobular glomerulonephritis commonly succumbed while still in the "nephrotic phase" to intercurrent infections before sufficient time had elapsed for complete evolution of the membranous or lobular glomerulonephritis into the sclerosing glomerulonephritis.[26] At autopsy the kidneys of such patients were found to be large, yellowish and without appreciable surface granularity; that is, they would possess the features common to kidneys from patients dying with the nephrotic syndrome of whatever cause. Although chronic membranous and lobular glomerulonephritis, as indicated, are seen less frequently at autopsy in these days of antibiotic therapy, there are observed a great many instances of intermediate as well as final stages in the transformation of chronic membranous and lobular glomerulonephritis to sclerosing glomerulonephritis.* The superimposed renal sclerosis, the occurrence of which was long ago appreciated by Volhard and Fahr,[27] and recently re-emphasized,[1,28] is manifested morphologically by progressive obliteration of glomerular capillaries, appertaining tubular atrophy, interstitial fibrosis, arteriolo- and arteriosclerosis and reduction in the over-all size of the kidney with the development of a diffuse, fine granularity of the so-called secondarily contracted kidney. (Figs. 28 to 31.) At the same time there tends to occur a parallel reduction in proteinuria, an "attempt" at compensatory polyuria with a lowered specific gravity of the urine instead of oliguria with a concentrated urine, a loss of edema, the appearance or increase of hypertension, lowering of the blood levels of the alpha and beta globulins with an elevation of the gamma globulins, along with a feeling of improvement on the part of the patient, until finally renal decompensation takes place terminating with death in uremia in about 40 per cent of patients within five years.[29] The hypertension has been attributed to ischemia caused by glomerular sclerosis[29] but, in reality, sclerosis of the afferent arterioles and intralobular arteries is also commonly present. The tempo of the sclerosis is highly variable but more than a dozen years may apparently

* Even those observers who concede that membranous glomerular changes may occur in some cases of lipid nephrosis insist that these are not inflammatory changes and hence should not be classed as glomerulonephritis. Acute membranous glomerulonephritis is, in reality, a variant of fibrinoid alteration, a change which cannot be properly dissociated from the broad process of inflammation. Cellular exudate, of course, is one but not the only manifestation of inflammation. Moreover, acute membranous glomerulonephritis is often either accompanied or succeeded by cellular exudation and, as mentioned, by fibrosis ultimately, just as are other inflammatory reactions. Therefore, to segregate this lesion, associated with the nephrotic syndrome, from glomerulonephritis would appear unwarranted, even semantically.

elapse before this process of sclerosis is initiated; as judged by clinical histories in some patients, the sclerosis may appear not to have progressed very far even after a quarter of a century.[30]

What, then, is the histologic difference between the late, sclerotic stage of membranous or lobular glomerulonephritis and the late stage of the more common, so-called "type I" hemorrhagic or azotemic glomerulonephritis? The answer is perhaps best given photographically, as in Figures 28 to 35. In those instances in which the nephrotic syndrome appears at the initiation or later in the evolution of the clinical picture, it is usual to find unmistakable and numerous stigmas of membranous or lobular glomerulitis. (Fig. 31.) These stigmas are identifiable even when accompanied by severe, partially obliterative sclerosis of the glomeruli with atrophy and fibrosis of tubules and marked granularity and reduction in size of the kidneys. On the other hand, in the kidneys of patients who presumably never had the nephrotic syndrome but who died with the clinical diagnosis of chronic glomerulonephritis ("type I"), the stigmas of membranous and lobular glomerulonephritis are either absent altogether or, if present, are relatively inconspicuous in contrast, as stated, with those sections from patients who had had lipid nephrosis ("type II") some time in their past. That is to say, the individual glomerular changes responsible for the nephrotic syndrome do not constitute an all-or-none phenomenon any more than the presence of only a few glomeruli with the lesions of diabetic glomerulosclerosis lead to the nephrotic syndrome. To put the concept still another way, "type I" and "type II" nephritis are not independent clinical and morphologic entities; rather, "type II"—i.e., lipid nephrosis—may and frequently does become transformed into "type I"; rarely, patients with the clinical picture of "type I" at the time of onset of their disease develop the clinical characteristics of "type II," as in the instances cited by Schwarz, Kohn and Weiner,[30] which first appeared as hemorrhagic glomerulonephritis and subsequently developed the signs and symptoms of lipid nephrosis. However, in these latter instances, in which even azotemia of short duration may occur, it is very likely that the lesion is a form of hemorrhagic membranous glomerulonephritis,[1] at times with superimposed, reversible exudative or proliferative glomerulitis and without distortion of glomerular architecture. This type of glomerular lesion is to be distinguished from the necrotizing glomerulonephritis which far more commonly is the basis for the diagnosis of severe hemorrhagic glomerulonephritis ("type I") and which, because of the marked derangement of glomerular architecture, could not produce the clinical complex of lipid nephrosis. (Figs. 8 to 10.)

Basis for Divergence of Views on the Nature of Glomerular Lesions in Lipid Nephrosis. Another phase of the long-standing conceptual disagreement that needs to be clarified is the fact previously alluded to; namely, that despite the author's conviction that in all cases with the nephrotic syndrome there are histologically detectable glomerular changes (the rare instance of bilateral renal vein thrombosis possibly excepted), other pathologists have failed to find any histologic changes of note in the glomeruli of an appreciable number of patients—especially children—who succumbed in the nephrotic stage of their disease. Admittedly, by its very nature, it is always difficult to answer this type of objection which pits the histologic findings of one observer against another. However, it is not altogether irrelevant to mention that the lesions of diabetic glomerulosclerosis were not recognized until 1936 even though they had been objectively described and illustrated before then; and, although recognized in 1936, they were regarded by many as non-specific and as occurring infrequently until otherwise proved some years later. This misconstruction of the diabetic glomerular lesion is mentioned because, despite its obvious specificity and easy identifiability, it had not only been overlooked for many years but even after its specificity appeared to have been documented adequately, completely divergent conclusions were subsequently recorded by workers of established competence. Another such instance is the marked disparity in the incidence of glomerulonephritis recorded in various infectious diseases; as, for example, the high incidence in subacute bacterial endocarditis and in the typhus fevers observed by some in contrast with the findings of others in more or less equivalent material.[6,31–33] Even more pertinent and perhaps more revealing of how relatively slight but significant glomerular changes may be dismissed or overlooked are the histologic observations reported on the kidneys of rats in which the nephrotic syndrome was produced with nephrotoxic sera. In an initial series of

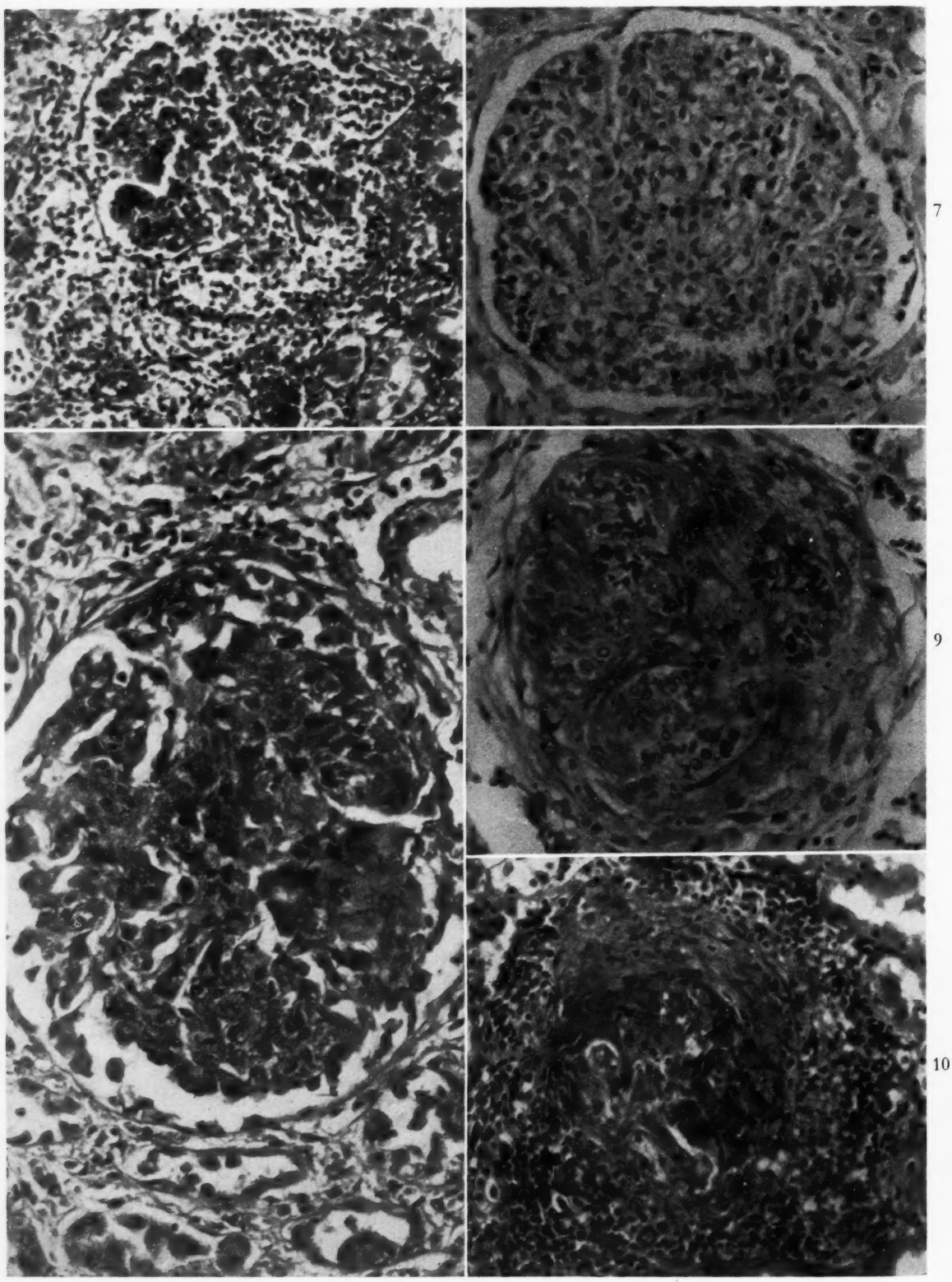

FIG. 6. Acute exudative glomerulonephritis caused by sulfathiazole; (hematoxylin and eosin, × 110).

FIG. 7. Acute proliferative glomerulonephritis; (hematoxylin and eosin, × 140).

FIGS. 8, 9 and 10. Acute necrotizing glomerulonephritis; (hematoxylin and eosin, × 560, 140 and 110, respectively).

experiments the glomeruli were recorded as showing no histologic change; in a subsequent series, in which the work was duplicated, glomeruli were rarely uninvolved and the characteristic changes of membranous glomerulonephritis were found. These discrepancies indicate that glomerular lesions may be disregarded by experienced observers often because they underrate the significance of intermediate degrees of change; changes, it should be again stressed, which are apparent even with routine hematoxylin and eosin stains.

In the matter of membranous glomerulonephritis, it appears to be a pivotal fact that comparatively less morphologic change is required in the capillary basement membranes of renal glomeruli of children to initiate proteinuria than is required in the glomeruli of adults. Accordingly, the relatively slight but meaningful degrees of thickening of basement membranes of the glomeruli of children are frequently labelled as within the range of normal because as a rule they do not approach the bent-wire appearance of correspondingly altered glomeruli of adults. (Figs. 11 and 26.) A careful comparison of these glomeruli with those from infants or children of identical age without renal disease helps sharpen the definition of the abnormailties. Moreover, in most sections of such kidneys evidence of frank glomerulitis with adhesion of loops to each other and to Bowman's capsules can be found in at least several glomeruli. (Fig. 12.) The same misapplication of criteria is also noted, in some reports, in the evaluation of the increase in number and size of the glomerular endothelial cells, both in the kidneys of children and, apparently, in the kidneys of the experimental animals. It is most likely that the marked disparity of prognosis in favor of children with the nephrotic complex is dependent on the lesser degree of organic, histologically evident change in the glomerular capillaries of these children. As a consequence, the glomerular changes in the children are more easily and more commonly reversible, as might be anticipated, than are the severer changes in the kidneys of adults. It is not to be inferred, however, that in some instances the membranous glomerulonephritis of children may not be fully as conspicuous histologically as any occurring in adults. The kidneys of a six year old child illustrated in Figure 29 demonstrate the terminal granularity and contraction brought about by such marked glomerular changes. What would be of fundamental importance to learn, of course, is the nature of the factors responsible for this kind of deviation in reaction in a given child. In view of the increasing number of agents that have been discovered to provoke membranous glomerulonephritis, and in view of the altered levels of complement, antistreptolysin titer, specific lipoproteins, etc., the precise factor or combination of potentiating factors which is involved in the production of the lesions is a vastly complicated enigma. The detailed correlation of such data with the glomerular lesions at autopsy is surely one of the requisities that could be met but is thus far lacking.

Etiology of Membranous Glomerulonephritis. It has been repeatedly suggested that the etiology of lipid nephrosis (that is, exclusive of the nephrotic syndrome due to diabetic glomerulosclerosis, glomerular amyloidosis and bilateral renal vein thrombosis) is quite different from that responsible for acute hemorrhagic glomerulonephritis ("type I") and that, as already mentioned, these two types are fundamentally different diseases. These conclusions warrant re-examination. It is true that overt infections such as tonsillitis, mastoiditis, scarlet fever, etc., are much more likely to precede acute hemorrhagic ("type I") glomerulonephritis than the other; occasionally, lipid nephrosis does follow such infections. It is also true that the antistreptolysin titer tends to be contrastingly low in lipid nephrosis. Finally, it is mentioned that in some cases, lipid nephrosis, unlike acute hemorrhagic ("type I") glomerulonephritis, may be caused by drugs (e.g., tridione) and that this fact further establishes the basic etiologic difference (Fishberg[4]). Actually, drugs (e.g., the sulfonamides) may also cause acute hemorrhagic glomerulonephritis of even a fatal variety.[1] Moreover, although the nephrotic syndrome may result from renal lesions of disseminated lupus erythematosus and of toxemia of pregnancy, these same disorders may provoke the clinical and histologic picture of hemorrhagic "type I" glomerulonephritis.[1] (Fig. 19.)

The fact remains, however, that in most instances of lipid nephrosis the etiology is obscure. This observation is not tantamount to the conclusion that the etiologic factors of lipid nephrosis ("type II") are fundamentally different from those of "type I" glomerulonephritis. Low-grade, clinically inapparent infections or immunologic responses to pre-existing infections

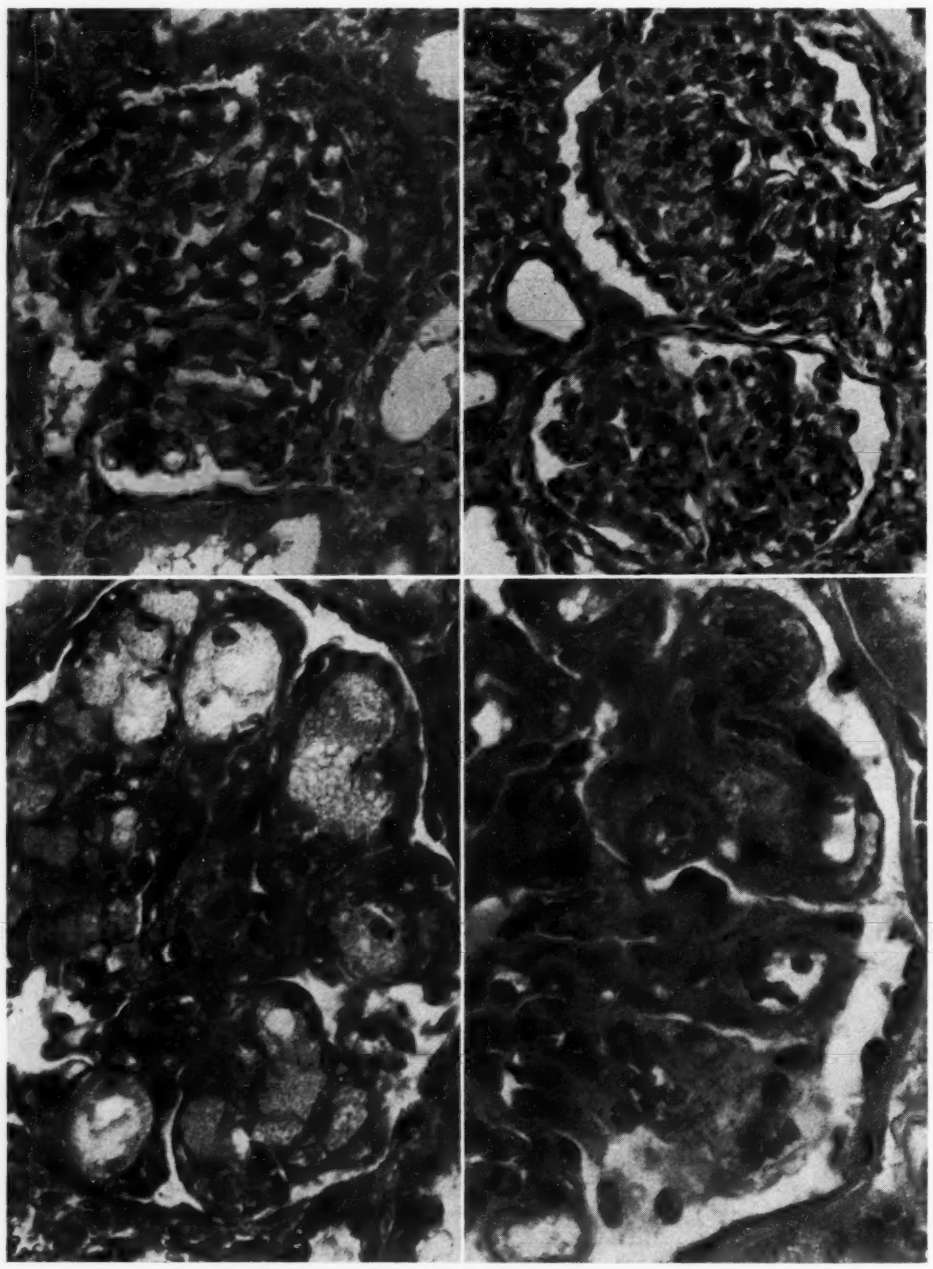

FIG. 11. Acute membranous (and proliferative) glomerulonephritis from a three and one-half year old child with the nephrotic syndrome, including 4+ proteinuria and an absence of hyaline droplets. Abundant protein precipitate dilates Bowman's space; (hematoxylin and eosin, × 280).

FIG. 12. Glomeruli from the same kidney as in Figure 11. The glomeruli show the fusion of loops to each other and to Bowman's capsule as well as the proliferation of capsular epithelium, which are usually found in a few scattered glomeruli even in "lipid nephrosis" of children; (hematoxylin and eosin, × 140).

FIG. 13. Fat-laden endothelial cells from an infant with the nephrotic syndrome; (hematoxylin and eosin, × 560).

FIG. 14. Acute membranous glomerulonephritis secondary to the use of nitrogen mustard, from a sixty-one year old Chinese with bronchogenic adenocarcinoma. This lesion, which was first noted in leukemic patients treated with nitrogen mustard, was not reproducible in leukemic mice treated with nitrogen mustard; (hematoxylin and eosin, × 560).

(including streptococcal infections) with altered antigen-antibody relationships on the basis possibly of an anemnestic provocation or of mechanisms as yet unknown, may be credibly hypothesized. It is a fundamental truth that the morphologic and immunologic response to an antigen or to a given organism or its products varies depending not only on the potency and dosage of antigen or infection but also on the antedating immunologic stimuli. An impressive illustration of this fact, as well as of the relationship of "type I and II" glomerulonephritis, is the experimental production of "type I" nephritis with a relatively weak nephrotoxic rabbit anti-rat-kidney serum and of "type II" with a larger amount of serum or a more potent but qualitatively identical serum.[34,35] An additional case in point is the variable renal response—necrotizing nephrosis, "lipid nephrosis" and "hemorrhagic glomerulonephritis"—all to poison oak dermatitis.[10] The very fact that the ASL titer is likely to be lowered in membranous glomerulonephritis does not necessarily constitute evidence, for example, of dissociation of the streptococcus from the nephritis any more than either the anergy to tuberculin precludes the existence of active tuberculosis or the low ASL titer in one phase of rheumatoid arthritis and its high titer in another,[36] or the depression of serum complement in the acute as opposed to the chronic phase of glomerulonephritis, constitute evidence of a different etiologic factor in these stages. The correlation between the elevated antistreptolysin titers on the one hand and the duration and severity of rheumatoid arthritis on the other,[36] is not only what might have been anticipated but may very well be analogous to what occurs in membranous glomerulonephritis. That is to say, membranous glomerulonephritis in many instances may be considered to correspond to a morphologically as well as immunologically less "severe" response to a streptococcal infection than is observed in "type I" glomerulonephritis; in other instances, other kinds of bacteria, treponemas, rickettsias, and perhaps viruses, and, to be sure, even hormones and a variety of drugs—the latter probably in the role of haptens—may also be involved in the production of this relatively bland glomerular change referred to as membranous glomerulonephritis. It is not as if the organisms involved in membranous glomerulonephritis produced their damage by direct invasion of the glomerular walls; it is far more likely that they are effective through the action of their toxic or antigenic products. A collateral or transitional phenomenon, which helps account for the essential pathogenetic unity of the various forms of glomerulonephritis, is the concomitant occurrence or superimposition onto membranous glomerulonephritis ("type II") of acute exudative, acute proliferative or acute necrotizing glomerulonephritis, as illustrated in Figure 32. As would be expected, in such instances the ASL titer might rise markedly as it did in the case just referred to, and the nephrotic syndrome might co-exist for a while with hematuria, hypertension and azotemia, at least until the membranous factor was morphologically and thereafter clinically neutralized. In other words, it is suggested that "type I" and "type II" glomerulonephritis represent not diseases *sui generis* but, rather, different grades of response to a variety of stimuli, which in many instances are similar qualitatively. In point of fact, the titer of serum complement is low in both acute hemorrhagic glomerulonephritis ("type I") and in membranous glomerulonephritis ("type II"), again suggesting that an active antigen-antibody reaction occurs in both.[37–39] Probably for a similar reason, the level of serum complement happens also to be depressed in disseminated lupus erythematosus and in cases of severe serum sickness.

SPECIAL VARIETIES OF MEMBRANOUS GLOMERULONEPHRITIS

Eclampsia. In addition to the over-all group of lipid nephrosis due to membranous glomerulonephritis there are several specific clinical entities in which membranous glomerulonephritis, or a variant thereof, plays a prominent part. These are eclampsia, disseminated lupus erythematosus and, rarely, diffuse scleroderma.[1] Membranous glomerulonephritis due to x-radiation also belongs in this special group. (Figs. 15, 18 and 19.)

Eclampsia may be associated with a large variety of renal lesions[1] but the most common is membranous glomerulonephritis. The membranous glomerulonephritis of eclampsia, for the clarification of which in this country Bell[40] is largely to be credited, is another example of a diffuse, usually acute, form of the lesion again characterized by marked proteinuria. There is reason to believe that a woman with a background of membranous glomerulonephritis in childhood, especially with a persistent, even

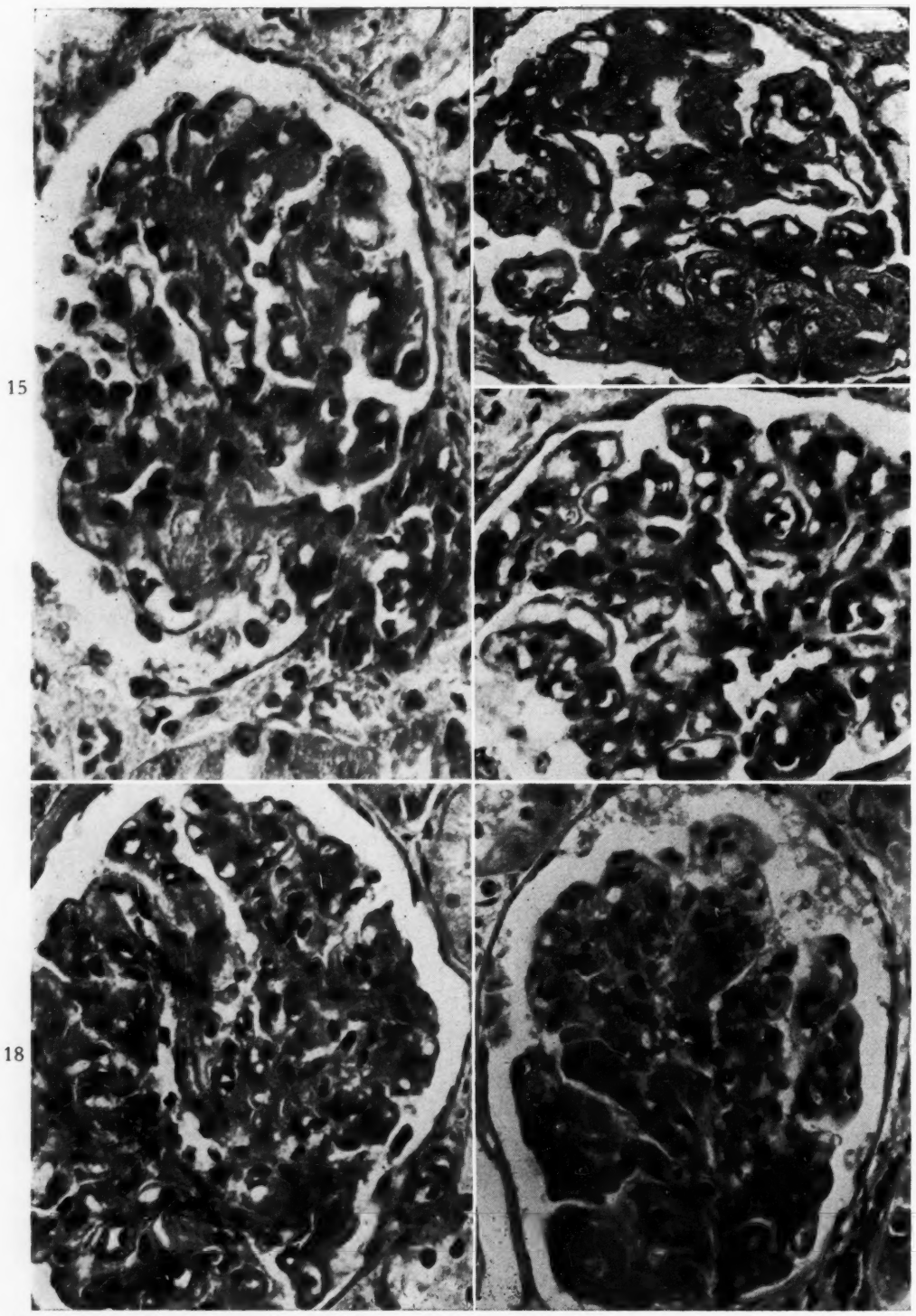

FIG. 15. Acute membranous glomerulonephritis in a three year old child, six months after postoperative x-radiation (2170 r) to the abdomen for a Wilms' tumor; (hematoxylin and eosin, × 560).

FIG. 16. Acute membranous glomerulonephritis from a patient with hepatic metastases secondary to rectal adenocarcinoma, treated with 6-mercaptopurine; (hematoxylin and eosin, × 280).

FIG. 17. Acute membranous glomerulonephritis following the use of nitrogen mustard in the adjuvant therapy of bronchogenic adenocarcinoma; (hematoxylin and eosin, × 280).

FIG. 18. Acute membranous glomerulonephritis of eclampsia; (hematoxylin and eosin, × 280).

FIG. 19. Focal acute membranous glomerulonephritis of disseminated lupus erythematosus showing the characteristic "wire-loop" lesions along with focal exudative glomerulitis; (hematoxylin and eosin, × 280).

mild hypertension, bears a predisposition to recrudescence of this form of lesion during pregnancy. The clinical elements of the nephrotic syndrome of eclampsia or "toxemia of pregnancy" are especially frequently modified by the severity of the glomerular membranous lesions with resulting encroachment onto the capillary lumens, the deposition of fibrinous thrombi, as well as an association with acute exudative and proliferative glomerulitis. In the less severe cases there may be complete reversal to normal within a few days following parturition. It is of interest that membranous glomerulonephritis may appear during pregnancy notwithstanding the fact that the level of ACTH, a modality often effective in the treatment of this disorder, is normally elevated over that of nonpregnant individuals. Perhaps relevant to the whole matter of the persistent difference of opinion regarding the presence of glomerular lesions in the classic cases of lipid nephrosis, particularly those of childhood, is the fact that for years many observers denied the occurrence of such membranous changes in the glomeruli of patients with eclampsia—and some still do[41]—although Bell[9] was able to detect them in fifty-one of fifty-two cases.

Lupus Erythematosus. It is well known that in a high percentage of cases of disseminated lupus erythematosus with clinically significant renal involvement (approximately 33 per cent) the nephrotic syndrome develops. The basis for the lipid nephrosis happens to be a special variety of membranous glomerulonephritis. Rarely, as stated, this lesion is observed in diffuse scleroderma. Unlike the characteristically uniform, diffuse thickening of all glomerular capillaries of diffuse membranous glomerulonephritis, the lesions of disseminated lupus erythematosus are almost always focal, involving some segments of the capillaries of a single tuft while sparing other capillaries of that tuft. (Fig. 19.) Moreover, frequently many glomeruli are completely spared. In addition, the focal fibrinoid degeneration often assumes the pattern of verrucal intraluminal thickening—a change that has been mistaken for thrombosis but really is analogous to the fibrinoid alteration that has been noted in the glomeruli of sensitized rabbits treated with cortisone[19] (Fig. 23) or to the lesions of thrombocytopenic verrucal angionecrosis (so-called "diffuse platelet thrombosis").[1] However, although thickened, these basement membranes so altered are excessively permeable to proteins, as previously mentioned. Therefore, if a sufficient number of glomeruli are thus involved there results a protracted proteinuria of a degree required for the appearance of the nephrotic syndrome, including the appearance of lipid in the tubules. This quantitative relationship between the extent of the glomerular involvement and the appearance of the clinical picture of lipid nephrosis obtains also in the case of diabetic glomerulosclerosis and glomerular amyloidosis. In a somewhat modified sense this same quantitative relationship applies also to the diffuse membranous glomerulonephritis in those many instances in which the initially widespread, abnormally permeable capillary surface is reduced by the superimposition of sclerosis, as well as exudative and proliferative cellular reactions, until the proteinuria disappears or is reduced to inconsequential amounts.

MORPHOLOGIC BASIS FOR DISPARITIES IN CLEARANCE STUDIES

If the basic glomerular change of membranous glomerulonephritis were the only one of any consequence present, supernormal clearances might be anticipated, and they are actually recorded in many instances. However, great variation in clearances occur, apparently independent of the normal lability of renal functions in children. Some of the reasons for these discrepancies will be discussed.

The Tm_{PAH} (Tm = maximal rate of tubular excretion of p-aminohippuric acid), the filtration fraction (FF), the urea clearance, and the glomerular filtration rate (GFR) all tend to be elevated above normal in what is clinically considered to be uncomplicated or "pure" lipid nephrosis. For example, Emerson and his colleagues[42] state that in about 42 per cent of children with lipid nephrosis the values for urea clearance were greater than 140 per cent of normal and in one child ranged between 200–300 per cent of normal for approximately six years. However, increased renal activity is not always present; the GFR in children with the nephrotic syndrome may range from 15 to 134 per cent of normal, to cite the experience in one series.[43] Supernormal clearances are much less likely to occur among adults with lipid nephrosis. Moreover, in "nephrotic children, renal function may swing in short periods from supernormal to subnormal levels and back again" (Smith[44]).

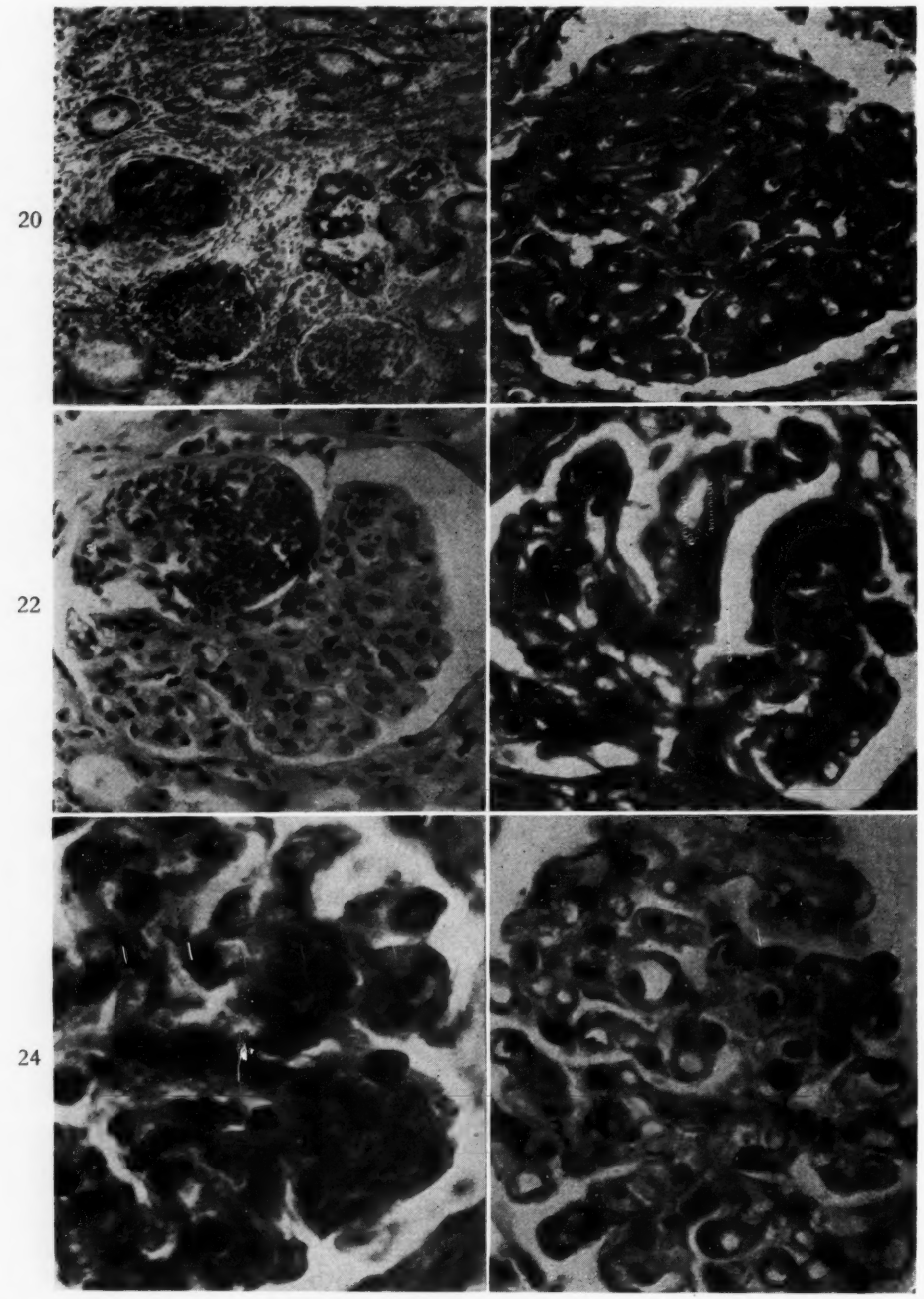

FIG. 20. Acute membranous glomerulonephritis following the use of cortisone for periarteritis nodosa. The lipid is conspicuous in glomeruli and proximal convoluted tubules; (oil red 0, × 96). (From: *Arch. Path.*, 52: 145, 1951.[11])

FIG. 21. Acute membranous glomerulonephritis following therapy with cortisone after bilateral adrenalectomy for carcinoma of the breast of a forty-seven year old woman.

FIG. 22. Aneurysmal dilatation of a glomerular capillary from a fifty-three year old man with clinically undiagnosed atrophy of adrenal glands; (hematoxylin and eosin, × 280). This lesion appears identical with that noted in patients dying of snake-bite (viper). (Latter slides seen through the courtesy of Dr. J. Caspar, of Petah-Tiqva, Israel.)

FIG. 23. Focal fibrinoid degeneration of a glomerular capillary from a rabbit treated with cortisone; (hematoxylin and eosin, × 280).

FIGS. 24 and 25. Acute membranous glomerulonephritis produced in rats with nephrotoxic anti-rat kidney rabbit serum; (hematoxylin and eosin, × 560). Figure 24: NPN 177, serum protein 4.8 gm. per cent, cholesterol 450 mg. per cent, total lipid 2,200 mg. per cent. Figure 25: serum protein 2.7 gm. per cent, cholesterol 400 mg. per cent, total lipid 3,090 mg. per cent. (The histologic slides and data were supplied through the generosity of Drs. Walter Heymann and Donald B. Hackel of Western Reserve University.)

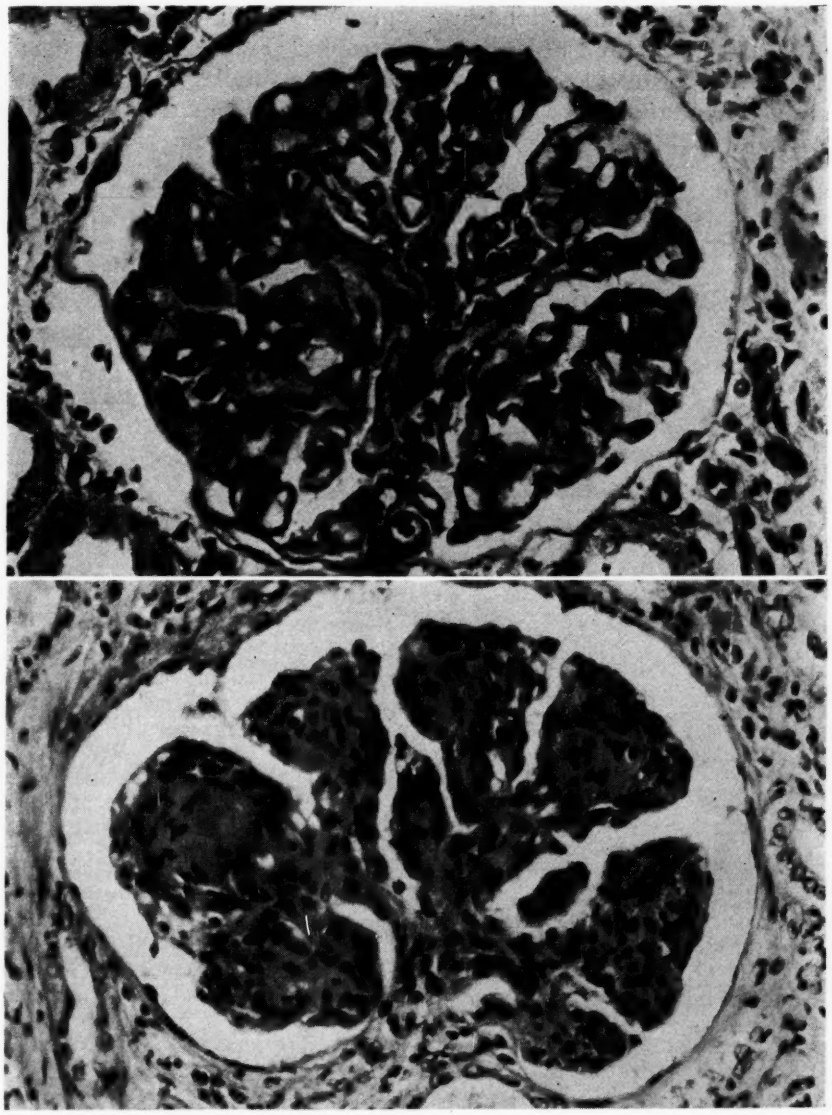

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FIG. 26. Chronic membranous glomerulonephritis from a forty-four year old man with the nephrotic syndrome of almost one year's duration; (hematoxylin and eosin, × 560).

FIG. 27. Chronic lobular glomerulonephritis from a twenty-six year old man with the nephrotic syndrome for nine months and a terminal picture of hypertension, anemia and azotemia; (hematoxylin and eosin, × 560). In the absence of diabetic glomerulosclerosis, glomerular amyloidosis and bilateral renal vein thrombosis, it may be assumed that a patient with the nephrotic syndrome has either of the two types of glomerular lesions pictured in Figures 26 and 27.

It would appear that, insofar as the kidney is concerned, the principal reasons for these wide variations are that, in addition to the primary change in the glomerular basement membranes, the several other possible histologic alterations previously mentioned may occur concomitantly or may be superimposed later in the course of the disease. These are changes which in varying degrees compromise the capillary lumens and alter the glomerular hemodynamics so as to modify the clearance studies in various directions. Such changes, already alluded to, include (1) an increase in size and number of the endothelial cells, (2) the presence of thrombi, (3) swelling of the capillary basement membrane with encroachment on the lumen (especially in lupus erythematosus), (4) progressive fusion and sclerosis of glomerular capillaries with obliteration of their lumens as part of the natural evolution of membranous glomerulonephritis, (5) transfor-

mation of membranous into lobular glomerulonephritis, and (6) superimposition at various times of several possible histologic forms of acute focal or diffuse exudative, proliferative or necrotizing glomerulitis. (Figs. 6 to 10.)

glomerular sclerosis occurs, the resulting tubular atrophy (Fig. 31) effects a corresponding decrease in tubular activity.

In summary, therefore, disparities in the results of clearance studies of different patients

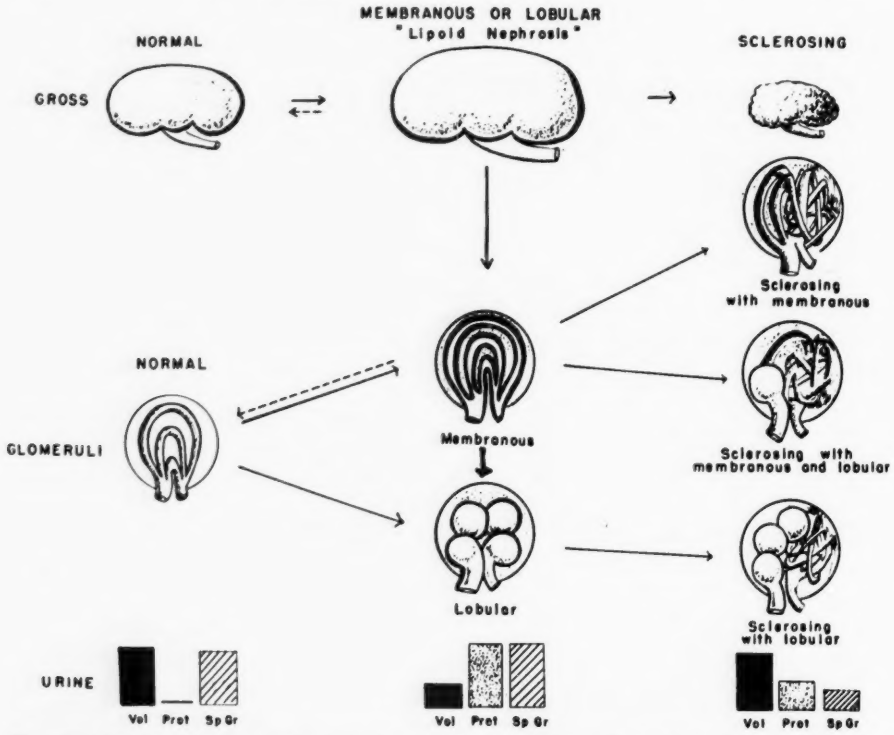

FIG. 28. Diagrammatic representation of the evolution of membranous and lobular glomerulonephritis to the sclerosing glomerulitis of the contracted kidneys paralleled by the gradual disappearance of the nephrotic syndrome and the development of progressive renal insufficiency.

It has been suggested that when the ratio $\frac{GFR}{Tm\ PAH}$ is low, a glomerular lesion is likely to be present.[44] Another interpretation of a low $\frac{GFR}{Tm\ PAH}$ in "pure" lipid nephrosis is that it is caused by "hypertrophy of tubules" resulting in a relative increase of tubular activity.[45] The validity of this latter conclusion may be questioned. The so-called "hypertrophy" of tubular cells associated with the nephrotic syndrome is hardly equivalent to the true hypertrophy (and hyperplasia) that occurs, for example, in the remaining kidney following unilateral nephrectomy. There is no reason to believe that in lipid nephrosis the mere enlargement of tubular cells by virtue of their increased content chiefly of water, lipids and perhaps absorbed proteins contributes to "glomerulotubular imbalance" by an accelerated rate of their functional activity. Of course, when narrowing of the lumens by

with the nephrotic syndrome or of the same patient at different times are in large measure mechanistically accountable for by the dynamic, morphologic, principally glomerular, variations described. These morphologic details are emphasized because it is felt that much of value is lost from the elaborate and painstaking studies of clearances, electrolytes, proteins and lipids for the reason that they are frequently matched by such non-descript uniformative histologic diagnoses as "chronic nephritis," not to mention the large number of reports by pathologists of "normal kidneys" in patients dying with the nephrotic syndrome who, in reality, had lesions of membranous glomerulonephritis.

MECHANISMS OF EDEMA AND DIURESIS IN LIPID NEPHROSIS

General Considerations. As stated previously, and as is generally agreed, the loss of protein in the urine is the constitutive factor in the

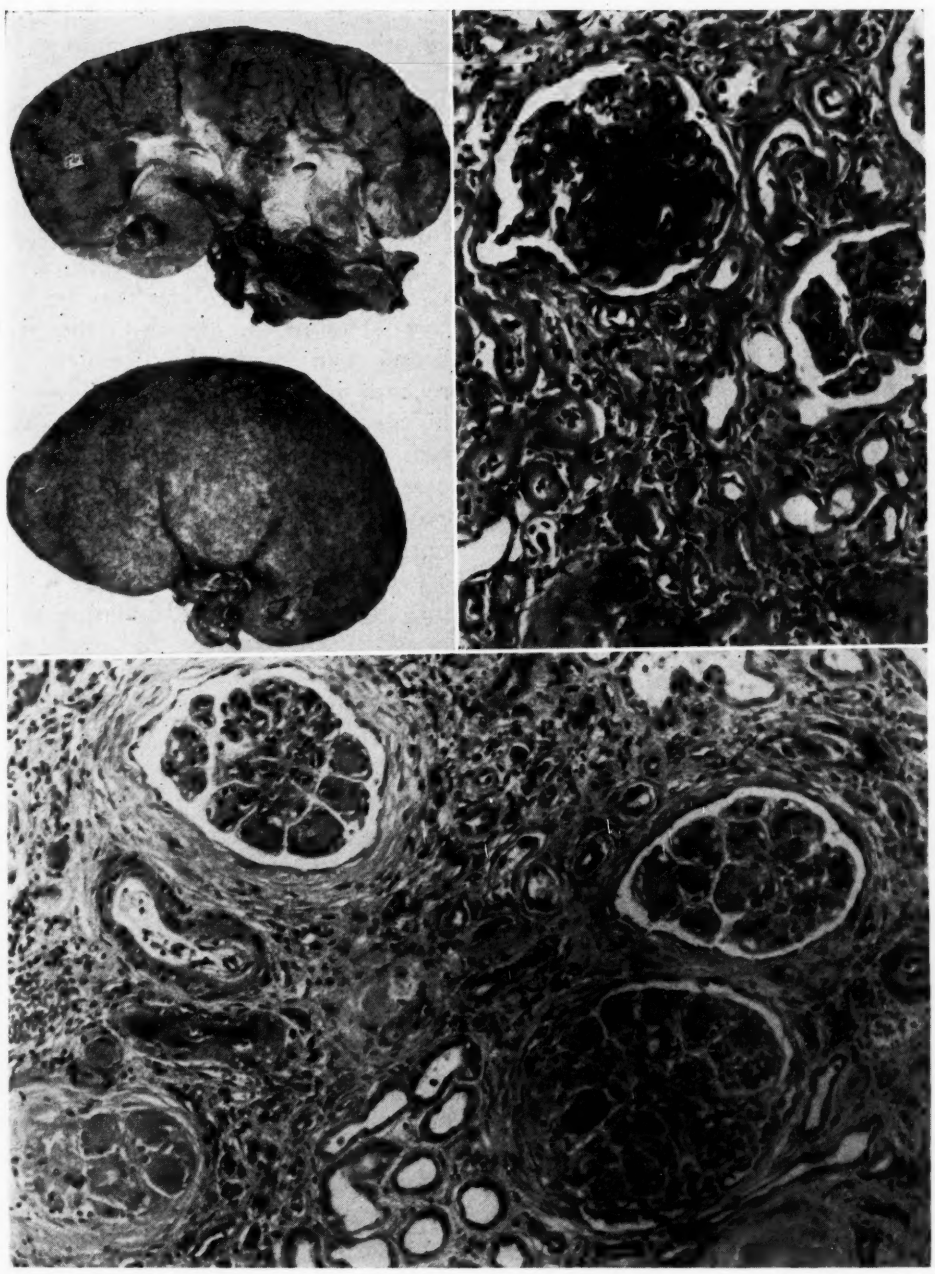

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FIG. 29. Granular contracted kidney from a six year old child with the nephrotic syndrome beginning at the age of three. In the last year of life the nephrotic syndrome disappeared and was replaced by renal insufficiency, malignant hypertension and malignant nephrosclerosis, superimposed onto chronic membranous glomerulonephritis. (From ALLEN, A. C. The Kidney. New York, 1951. Grune & Stratton Inc.)

FIG. 30. Renal amyloidosis with contraction and loss of the nephrotic syndrome; (hematoxylin and eosin, × 110).

FIG. 31. Chronic sclerosing glomerulonephritis, an end stage of chronic lobular glomerulonephritis of which some histologic evidence is still detectable. The patient was twenty-four years old at the time of death and had had the nephrotic syndrome following toxemia of pregnancy six years previously; blood pressure 240/140; (hematoxylin and eosin, × 110).

development of the edema of lipid nephrosis. The unadorned explanation commonly offered is that the depletion of plasma proteins, especially of albumin which has a comparatively low molecular weight, reduces the colloid osmotic pressure of the plasma so that water is released to the tissue spaces and body cavities in response to the physical laws of "iso-osmosis." While there can be little justifiable doubt that the hypoproteinemia and edema of lipid nephrosis bear an initiating, pathogenetic relationship to each other, the nature of that relationship—its dynamics and the physiologic composition of its family—is not simple and direct. In the first place, one of the barriers in the final exposition of the problem is that of methodology. For example, it is clear that in the determination of the osmotic pressures of fluids considerable discrepancies exist between the results obtained by theoretic computation based on the concentrations of various components of the fluids, (e.g. the Scatchard equation) and those obtained by direct measurement of osmotic pressure with laboratory instruments, especially since the instruments generally used are stated to show a wide range of error.[46] Secondly, although an over-all positive correlation is found between the presence of edema and of hypoproteinemia, the number of exceptions as well as the spontaneous or therapeutic initiation of diuresis and the reduction of edema without appreciable modification of the concentrations of plasma proteins require further explanation. Finally, the physiologic "incongruities" observed in other disorders in which edema occurs, notably the edema associated with starvation, need to be reconciled. It is almost universally assumed that the edema due to starvation is the result of diminished colloid osmotic pressure of plasma caused by depletion of dietary and plasma protein. However, it has been found that "although hypoproteinemia was common in famine areas, it was generally slight in degree and was not closely related to the appearance or severity of edema" (Keys et al.[47]). Moreover, in the production of experimental edema among volunteers without renal or cardiac failure it was observed that "the plasma protein concentration fell only slightly and the A/G ratio remained within normal limits."[47] Since what are termed physiologic "incongruities" are naturally manifestations of an incomplete supply or inventory of the facts, it might be expected that the disparities between degrees of hypoproteinemia and edema would be found to be created by compensatory or secondary lines of homeostatic defense; that is, compensatory or secondary so far as lipid nephrosis is concerned, but primary in other situations. Chief among these reserve factors are electrolytic balances, and probably also the neurohypophyseal antidiuretic hormone (ADH); the role of the vasodepressor material (VDM, ferritin) in the control of ADH[48] requires additional documentation. The following data and hypotheses illustrate this thesis.

Edema. That the renal control of absorption of water and electrolytes may be an augmentative factor in the edema of the nephrotic syndrome can hardly be doubted. It has been recently and authoritatively stated by Eder and his associates[49] that the edema in the nephrotic syndrome is the result of renal tubular absorption of water as well as sodium and chloride ions in excess of that required for the maintenance of normal extracellular volume. This imbalance is attributed to a decrease in GFR ("glomerular insufficiency") or to stimulation of the tubular activity resulting in "primary tubular preponderance" with consequent excessive absorption as indicated. However, in contradiction, it is clear that edema may accumulate and persist despite a normal or even supernormal GFR so that the diminished filtration rate can hardly be the basic factor involved. The concept of excessive absorption of Na^+, Cl^- and water through primary and specific tubular activity toward these materials is not altogether credible as an explanation of the basic mechanism of the edema in the nephrotic syndrome. Nor does this concept acquire much reinforcement from the interesting collateral hypothesis that the hypoalbuminemia of the nephrotic syndrome brings about a transfer of fluid from plasma to the interstitial space, resulting in a decreased plasma volume and potential circulatory insufficiency which, in turn, stimulates the secretion of antidiuretic hormone and adrenal cortical steroids. The latter, finally, are presumed to be the cause of the excessive tubular reabsorption of Na^+, Cl^- and H_2O.

Another suggestion concerning the role of the kidney is that sodium retention is the renal response to prerenal electrolytic deviations dependent principally on the failure of cells to transport or retain potassium rather than to renal dysfunction (Metcoff et al.[50]). In other words, deviations in the distribution of potassium between cells and interstitial fluid, in

accordance with this hypothesis, is presumed to be the primary electrolytic disorder rather than sodium imbalance. The intravenous administration of sodium chloride to patients with the nephrotic syndrome is followed by an excessive excretion of potassium, in contrast with what happens in normal individuals. Depletion of potassium from tissues is thought to occur in the nephrotic syndrome as intracellular protein is used to replace the diminished plasma protein. The resulting intracellular protein deficit is presumed to release a corresponding quantity of potassium for excretion in the urine. With peripheral water retention following lowered plasma osmotic pressure, the lowered osmolarity of both the intra- and extracellular fluids would be maintained unless elevated by an increase in the concentration of solutes. This is achieved by the renal retention of sodium followed by transfer of sodium into the cells, or by the transfer of fluid from the cells, with maintenance of the iso-osmotic balance between interstitial fluid and cells. In other words, stated somewhat teleologically, the kidney removes potassium from the plasma in order to avoid excessive concentrations of toxic potassium; correspondingly, it withholds sodium in order to help achieve the optimal osmolarity of body fluids. The precise role of ACTH and other agents in initiating diuresis in the nephrotic syndrome is still far from fully defined but it is known that ACTH may yield an exaggerated excretion of potassium[50] in harmony with the hypothesis just outlined.

Undoubtedly, other forces must apply in the homeostatic organization of body fluid but the foregoing suggestions are pertinent and of additional use in that they properly remove from the renal tubules the kinds of theoretic dysfunctions long attributed to them, endowing them, instead, with a remarkably faithful vitality.

Diuresis. In view of the likelihood that the edema of the nephrotic syndrome is dependent on more than one echelon of physiologic adjustment—that is, first on the hypoalbuminemia, and then on the electrolytic balances that have been forced into compensatory play—it is of importance to learn the mechanism of the reverse response, namely, diuresis. What takes place homeostatically during the diuretic response to such therapeutic modalities as ACTH or cortisone? Presumably similar biochemical alterations occur spontaneously or after certain infections such as measles. Diuresis in lipid nephrosis may occur as early as the fifth day of an eight-day course of treatment or as late as four days following the completion of the course. It is widely assumed that the key event promoting diuresis is the retarded tubular absorption or increased excretion of sodium. That this increased output of sodium takes place has been proved, but it is also true that many other physiologic changes occur concomitantly. These include depression of the level of alpha and beta globulins with a rise in gamma globulins, a rise in titer of serum complement, often, but not always, some increase in concentration of serum albumin, excessive excretion of potassium, and an increase in the glomerular filtration rate (GFR, mannitol or inulin clearance).[45,50] The increase in the GFR may well be the result of post-therapeutic restoration of the normal size of the lumens of the glomerular capillaries perhaps through reduction in the size and number of the endothelial cells and epithelial cells, and in the thickness of the swollen basement membrane. The permeability of the basement membrane, as judged chiefly by the diminished excretion of protein, is also usually restored to its normal quality after successful treatment. However, as mentioned, diuresis in lipid nephrosis may occur without appreciable elevation of the serum albumin or decrease in proteinuria so that these components cannot be the immediate or trigger factors in the diuresis. Moreover, although an increased excretion (or decreased rate of destruction) of antidiuretic hormone has been noted in lipid nephrosis,[51] it is likely that changes in concentration of this hormone are dependent on or secondary to other stimuli, perhaps of the kind previously outlined which affect homeostasis. The dearth of data on the mechanism of renal action of antidiuretic hormone, including the possibility of whether or not ACTH and cortisone inactivate it, puts evaluation of its role on a speculative level, as already mentioned. This same sparsity of information to date also makes it difficult to understand why some patients respond at one time and not at another, why some never respond despite the fact that their renal functions, and presumably the renal lesions, match those of patients who are treated successfully, and exactly why the duration of the response, both therapeutic and spontaneous, varies over the broad period of from two to three months to over a year. It is of further interest that hematuria, mild azotemia and hypertension do not necessarily preclude the occurrence of

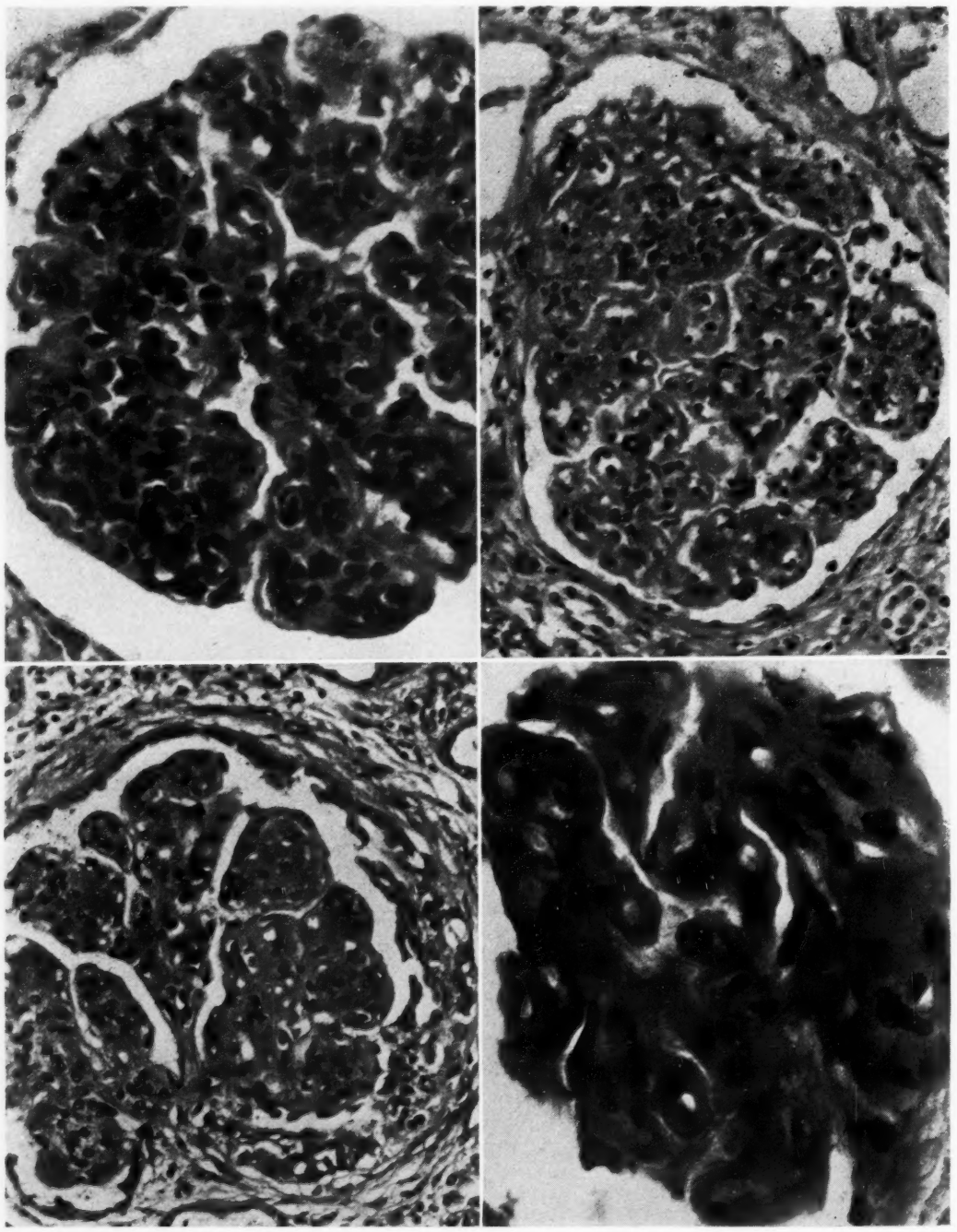

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FIG. 32. Acute membranous glomerulonephritis with superimposed or, at least, coexisting acute exudative glomerulonephritis; (hematoxylin and eosin, × 560). The patient was a forty-three year old man with generalized anasarca of eleven months' duration, blood pressure 190/90, serum albumin 1.8 gm. per cent, globulin 2.7 gm. per cent, 4+ proteinuria, ASL titer 420 units, cholesterol 260 mg. per cent, B.U.N. 160 mg. per cent, 10 to 12 white blood cells and 3 to 5 red blood cells per high power field in the urine; death in uremia.

FIGS. 33 and 34. Transformation of membranous into lobular and sclerosing glomerulonephrits; (hematoxylin and eosin, × 200). The patient was a thirty year old man whose "pure" nephrotic syndrome was first manifested ten years previously. In the last year the blood pressure mounted steadily and death in uremia occurred after the development of malignant nephrosclerosis.

FIG. 35. Sclerosis of membranous glomerulonephritis, from a twenty-nine year old man with a nephrotic syndrome of two years' duration; (hematoxylin and eosin, × 560).

diuresis. It may be reasonably assumed that in these latter instances distortion of glomerular architecture has not yet taken place, even though these signs might so indicate.

Mechanism of Action of Therapeutic Agents. If membranous glomerulonephritis and its glomerular sequelae are in fact the basic organic denominator of all instances of lipid nephrosis (exclusive of diabetic glomerulosclerosis, glomerular amyloidosis and renal vein thrombosis) then there are two paramount objectives to be reached: (1) the reversibility to normal of the membranous glomerulonephritis and (2) in the event of failure to fulfill the first objective, to prevent the relentless, attritive development of the glomerular sclerosis inherent in the natural evolution of membranous glomerulonephritis. It is also for these purposes that complete inventory should be taken of the individual and correlative levels of at least such previously mentioned immunologically active components known to be altered (antistreptolysin, serum complement, lipoproteins, etc.) and carefully correlated with the renal lesions. It is again for reasons of these objectives that it becomes of crucial importance to know whether or not it is confirmable, as herein proposed, that all instances of lipid nephrosis are associated with glomerular lesions, and, further, that membranous glomerulonephritis is closely related in a broad sense, pathogenetically and etiologically, to other forms of glomerulonephritis.[1] As a corollary to these objectives it would be of revealing importance to know, when a remission is produced by ACTH, cortisone, nitrogen mustard,[52] measles, heparin[53] or whatever modality, whether or not that remission is accompanied by a reversion to normal of the glomerular changes, however temporary. Such a histologic regression would be anticipated if the thesis herein outlined is correct. The recent observation by Kramár[54] that cortisone increases the "strength" of capillary walls of skin, as measured by their resistance to applied suction, may be relevant. On the other hand, cortisone may weaken the walls of glomerular capillaries of rabbits (Fig. 23) and occasionally even of humans. (Fig. 20.) It is not yet understood precisely how or at what level of the scheme of reaction ACTH or cortisone or the other modalities act; that is, do they interfere in some way with antigen-antibody reaction either in body fluids or in the tissues themselves, possibly through an effect on serum complement, or by their inhibition of the formation of antibodies after the manner of nitrogen mustards or x-radiation; do they act directly on the abnormal tissues; or do they exert their effects as intermediate agents modifying other substances which in turn modify the tissues? There is definite evidence that ACTH and cortisone do have an effect on the delayed type of bacterial sensitivity inasmuch as either hormone, for example, may reduce or temporarily eliminate the reaction to intradermal tuberculin.[56] These hormones also have been clearly demonstrated to have a markedly ameliorating action on the clinical effects of hypersensitivity including cutaneous reactions to drugs, asthma, the elimination of positive patch tests, as well as the symptoms of allergic arteritis.[57,58] In lipid nephrosis of children the level of serum complement drops during cortisone therapy and rises with diuresis.[59] In addition, there is experimental evidence of the inhibitory effect of ACTH on the development of glomerulonephritis and cardiovascular lesions of hypersensitivity.[57] However, there are suggestive data indicating that these agents do not block the antigen-antibody reaction but act, perhaps, by altering the tissue response to the union of antigen and antibody. On the other hand, in disseminated lupus erythematosus, for example, ACTH and cortisone precipitate a rise in titer of serum complement, elevate serum albumin and reduce the level of gamma globulinemia. The latter is probably reflected in the diminution of the numbers of "L.E. cells."[58] It is of related interest that nitrogen mustard, which also has on occasion produced remissions in lipid nephrosis,[52] may itself inhibit the formation of antibodies.[55]

X-radiation is still another modality which not only may cause membranous glomerulonephritis in humans (Fig. 15) but also may inhibit the production of antibodies and of experimental nephrotoxic glomerulonephritis. In other words these agents (x-radiation, nitrogen mustards, cortisone as well as infections) are potentially biphasic in their action on the kidneys just as some agents, such as triethylene melamine, are both cancerogenic and cancerolytic. That is, these modalities may cause glomerulonephritis under certain conditions and help to prevent or relieve it under other conditions. Precisely what the potentiating factors are in each circumstance remains to be determined.

Hypercholesterolemia. Along with remissions following the use of ACTH or cortisone, there

is an associated reduction in the levels of hypercholesterolemia. This occurrence is of interest in view of the paradoxic observation that prolonged cortisone therapy in human beings produces an elevation in total serum cholesterol, free and esterified, as well as in the phospholipids.[60] On the other hand, the administration of cortisone, which causes a moderate hypercholesterolemia in normal rabbits, is said to depress appreciably the hypercholesterolemia resulting from the feeding of cholesterol to rabbits.[61]

The hypercholesterolemia has always been a poorly understood manifestation of the nephrotic syndrome. The relationship of hyperlipemia to renal injury will be considered shortly. Nevertheless, with the knowledge that heparin has the property of clearing lipemic plasma with reduction in the level of lipids, especially neutral fat,[62] determination of the effect of heparin on the course of experimental lipid nephrosis naturally suggested itself.[53] Lipid nephrosis was produced in rats by the administration of potent anti-rat-kidney serum. It was discovered that heparin had a profound influence on the development of the nephrotic state. When administered in the induction stage of the nephrosis, heparin suppressed completely, or almost completely, the appearance of ascites and anasarca, and reduced markedly the level of lipemia as judged by the controls. Discontinuance of heparin was followed by progressive rises in lipid levels. In the animals already made nephrotic heparin brought about a reduction in plasma lipids but did not appear to affect the degree of edema. The reduction in hyperlipemia is attributed to a change in the physicochemical state of lipids, thereby facilitating their removal by the liver. However, the mechanism by which heparin influences regression of the edema is unexplained although the known effect of heparin in lowering the level of serum complement in nephrotoxic nephrosis[63] inhibiting immunologic phenomena (e.g., the Shwartzman reaction[64]), and in altering the osmotic pressure of plasma,[65] may bear on the problem.

The direct answer to the far reaching question regarding the morphologic effect of the therapeutic agents in lipid nephrosis—and perhaps also to whether or not a beneficial response is to be anticipated—will not be available until biopsy specimens of kidney are obtained before and after therapy. For obvious reasons it is not likely that an adequate sample of such biopsy specimens of human material will be secured although this procedure is slowly acquiring more and more advocates. However, since the nephrotic syndrome has been produced in rats, this procedure would seem worth investigating from this viewpoint. It would also furnish a means of study of methods or agents—e.g., ACTH and cortisone, heparin, hyaluronidase, antihyaluronidase, collagenase and other possible inhibitors of the accretion of collagen—designed to prevent the progressive, mortal, obliterative collagenization to which such altered glomeruli are subject.

Net Survival Following Use of ACTH and Cortisone. As the situation is now surveyed, it is apparent that the dictum "ACTH and cortisone cure nothing" applies also to lipid nephrosis. Moreover, as with other diseases in which these agents effect dramatic periods of relief, the evidence is far from clear-cut that they appreciably prolong life from the viewpoint of group survival.[29] Undoubtedly in individual instances, these modalities, by inducing diuresis and tiding a patient over a period of exacerbation may for a while avert death just as they may in pemphigus, for example. However, there is no evidence that ACTH or cortisone modifies the ultimate evolution of the disease or that the number of cures following the use of these agents is significantly greater than that occurring without their use. The frequency of repeated "spontaneous" remissions and of remissions following infections, particularly measles, is in harmony with this conclusion. The survival rates for patients with lipid nephrosis without benefit of ACTH or cortisone have been variously reported as 5 to 12 per cent[2,66] to approximately 40 per cent.[26] Indeed, some patients may recover spontaneously after failure to respond to specific therapy.[29] The comparative evaluation of survival rates recorded at different clinics is not easily possible because of such variable factors as clinical and morphologic criteria for the definition of the disease, the kind of management, the type of antibiotics used, the length of follow-up, the ages of patients, etc. However, on the basis of the observation that about 43 per cent of adults and children treated with ACTH or cortisone or both have been apparently well for more than a year, Luetscher and his associates[29] raise the question of the superiority of these therapeutic agents over the results achieved by non-specific measures. Obviously, the therapeutic advance that has yielded more tangible

results in lipid nephrosis is the effective use of antibiotics in controlling the grave infections which used to be responsible for one of three deaths.[26] Furthermore, there is the grim fact that ACTH or cortisone may actually precipitate death in lipid nephrosis by their effects on electrolytes, by the contributory effects of atrophy of the adrenal glands from the use of cortisone, by the infectious processes abetted and masked by these hormones, particularly in the presence of low levels of gamma globulins (a source of antibodies), and by their production occasionally of malignant nephrosclerosis as well as aggravation of membranous glomerulonephritis.[11,67]

ROLE OF TUBULAR CHANGES IN LIPID NEPHROSIS

If glomerular changes are indeed the prime pathogenetic basis for the nephrotic syndrome, some explanation is due not only for the emphasis placed by many on the contribution of tubular lesions to this syndrome but also for the concept, shared even by Bell,[9] who did much to emphasize the existence of glomerular lesions in "mixed" lipid nephrosis, that in the "pure" form of lipid nephrosis no glomerular alteration is discernible with the microscope.

The tubules of kidneys associated with the nephrotic syndrome have had attention diverted to them because of two conspicuous changes within the epithelium of the proximal convoluted tubules: (1) the abundance of lipid, partially birefringent, principally in this same portion of the nephron, and (2) the hyaline or colloid droplets or granules. The epithelial fat, and with much less frequency, the hyaline granules are observed in the kidneys of patients with the nephrotic syndrome due to any of the previously listed diseases; namely, membranous or lobular glomerulonephritis, diabetic glomerulosclerosis, glomerular amyloidosis or bilateral renal vein thrombosis. Lipid, in these cases, is observed also in glomerular endothelial as well as epithelial cells. (Figs. 13 and 20.) Coupled with certain physiologic considerations which have already been outlined, it is natural to attribute serious derangement to structures that are so obviously altered microscopically. However, as is well known, a correlation need not exist between the dysfunction of a structure and the extent, or better, conspicuousness, of its morphologic change. One of many examples that could be cited as illustrative of this principle is the lack of causal relationship between dysfunction of an organ in hemochromatosis and the amount of hemosiderin within it. Moreover, in simple hemosiderosis of the kidney, such as follows paroxysmal nocturnal hemoglobinuria of long duration, the deposition of the pigment in the epithelium of the proximal tubules may be so extreme as to be prominent grossly, yet it causes no apparent dysfunction beyond a lowering of the renal threshold specifically for the excretion of hemoglobin. Actually, data on ammonia formation, urinary pH, phenosulphonphthalein clearance and Tm for diodrast and PAH do not suggest tubular dysfunction in "lipid nephrosis," although in some instances the renal threshold for glucose may be lowered. These examples are not altogether irrelevant to the thesis of the physiologic meaning of the fat and the hyaline droplets in the tubular epithelium.

Tubular Lipid. There is no evidence to suggest that the mere presence of the fat alters tubular function. In general, there is a close parallel between the hypercholesterolemia and the tubular lipid. This is not to say that either is necessarily the cause of the other although it would appear reasonable to assume that the renal fat in the nephrotic syndrome is caused chiefly by the absorption of excessive blood lipid from the glomerular filtrate, especially in view of the occurrence of hyperlipemia in experimental lipid nephrosis several hours prior to the appearance of fat in tubular epithelium.[68] That this simple explanation does not embody the complete answer is attested to by the fact that in the acute stage of membranous glomerulonephritis abundant tubular fat may be present without corresponding rises in levels of blood cholesterol, a finding infrequently noted in experimental lipid nephrosis. Parenthetically, it is also a fact that large amounts of lipid are normally present in the proximal tubular epithelium of cats (and dogs) without apparent elevation of the total plasma lipid or any of its components, in comparison with levels in other species.*[69] The possible occurrence of abnormal glomerular leakage of lipids or of lipoproteins in this early stage, prior to the development of hyperlipemia, and their possible subsequent

* Plasma lipid (mg. per 100 ml.) in cat: total lipid, 376; neutral fat, 108; total fatty acids, 228; total cholesterol, 93; cholesterol esters, 63; free cholesterol 30; phospholipid, 132 (Boyd, 1942).[69]

tubular resorption, is an additional phenomenon to be considered. Furthermore, it is an established fact that fatty change in proximal tubular epithelium of scattered nephrons may occur in conditions totally unrelated to the nephrotic syndrome, as in poisoning with phosphorus, chloroform, carbon tetrachloride, mercury, para-aminobenzoic acid or colchicine, in diabetes mellitus without diabetic glomerulosclerosis, and benign or malignant nephrosclerosis. In nephrosclerosis the fatty change is attributed to the appertaining glomerular ischemia; in the others, the renal fat is considered secondary to the elevated blood lipids. However, in none of these instances, it is generally agreed, is there evidence warranting the conclusion that the tubular fat is the cause of the proteinuria. In view of Opie's[70] observation that "injury of cells may bring about accumulation of visible fat," the contributory role of the renal ischemia in the production of tubular fat in lipid nephrosis may need to be re-evaluated. It might also be mentioned that in the past the accumulation of fat droplets within cells has been attributed to the lipid-containing mitochondria although this relationship could not be confirmed by Lewis and Lewis.[71]

The lipiduria which accompanies the nephrotic syndrome is contributed to by the leakage of lipids through abnormally permeable glomeruli as well as by the desquamation of lipid-laden epithelial cells. The appearance of fat droplets in the urine following spontaneous and experimental fat embolism does not necessarily imply that they have passed through normal glomeruli. For example, as a result of traumatic injury spontaneous fat embolism may be associated with shock and, accordingly, renal damage.

The basis for the hypercholesterolemia in the nephrotic syndrome is not understood nor does the vague teleological explanation that it may represent a compensatory "attempt" to restore the level of osmotic pressure of the serum clarify its pathogenesis. As stated, in the nephrotic syndrome an elevation of alpha and beta globulins occurs; to these lipids are bound in high concentration, especially to the beta globulins. The possibility that a primary disturbance exists in the lipid metabolism is not adequately supported by the evidence.[68] An additional consideration in the explanation of the genesis of the lipemia is the plain fact that diets low in protein lead to hypercholesterolemia. It would appear likely that the protracted loss of protein in the urine produces an equivalent effect. In any event, hypercholesterolemia is not caused merely by a depression or even absence of gamma globulins[72] nor is there reason to believe that hypothyroidism is related to the production of hypercholesterolemia in lipid nephrosis even though the basal metabolic rate may be lowered and administration of thyroid extract to physically normal patients results in a significant lowering of serum cholesterol and of Standard S_f 10–12, and S_f 12–20 lipoproteins.[73] Not only is it fairly well agreed that the lowered basal metabolic rate in lipid nephrosis is attributable to the subcutaneous cushion of anasarca, but it has also been shown that thyroid function, as measured by the uptake of radioactive iodine, is normal in patients with lipid nephrosis.[74]

Finally, a discussion of hypercholesterolemia and renal disease calls for reference to the fact that many types of experimental procedures damaging or otherwise affecting the kidneys have been followed by elevation of the blood lipids (neutral fats principally, as well as cholesterol and phospholipids). These procedures include poisoning with uranyl nitrate, mercury bichloride and potassium chromate, unilateral and bilateral nephrectomy, x-radiation, unilateral occlusion of a renal artery, and ureteral ligation.[68,75–77] The chemicals just mentioned (mercury bichloride, uranyl nitrate and potassium dichromate) cause histologically overt injury to the epithelium of the proximal convoluted tubules to which the hypercholesterolemia is attributed through mechanisms as yet unknown. Therefore, the question once again arises as to whether or not some other less apparent or submicroscopic form of tubular damage exists in lipid nephrosis. Inasmuch as so sensitive a tubular function as control of specific gravity—among several others—is often unimpaired in lipid nephrosis, it is difficult to imagine the existence of a kind of tubular injury in lipid nephrosis analogous to that in necrotizing nephrosis which might be linked to hyperlipemia. It is of significance that as glomerular sclerosis with tubular atrophy advances in membranous or lobular glomerulonephritis, the nephrotic syndrome tends to disappear and the hyperlipemia to be diminished in spite of added tubular damage, thus further complicating the understanding of the relationship of tubular damage and lipid metabolism.

Undoubtedly, in the past, an additional important block in the understanding of the pathogenesis of the hypercholesterolemia in the nephrotic syndrome has been the sparsity of information on the dynamics of lipid metabolism in general, a situation that is beginning rapidly to be corrected in fundamental ways. It was not long ago commonly accepted that most of the cholesterol, cholesterol esters and neutral fat circulated in the blood as free molecules clinically dissociated from other compounds. With the aid of electrophoretic studies a great many new facts have been harvested which have made it necessary to modify the basic concepts of lipid metabolism. One of these revelations is the fact that approximately two-thirds of the total plasma cholesterol is concentrated in the beta lipoproteins, which are especially concerned with their transport in the body; most of the remainder is bound to the alpha proteins.[65,78,79] Another revelation is that the plasma proteins are in dynamic equilibrium with a "metabolic pool" of amino acids. When a large portion of one component, say albumin, is lost, it is not as if a slice of plasma protein had been lopped off; rather, a complex compensatory readjustment takes place in the remaining proteins to meet the new physical, chemical and probably immunologic requirements. In other words, there exists a close linkage, actually a chemical union, between most of the plasma lipid and the plasma protein, as well as between all plasma protein and amino acids, so that the rise of levels of blood lipids in association with increased concentrations of lipid-rich beta proteins becomes a less fortuitous if still complex and unresolved phenomenon than it appeared to be when lipids and protein were thought to circulate as chemically free substances.

Hyaline Dropelets. Views of their nature and pathogenesis: Hyaline granules or droplets within the proximal tubular epithelium have long been identified with lipid nephrosis. However, their physiologic significance is still very much an unsettled matter. At one time they were thought to indicate the tubular excretion of protein.[80] Many observers currently believe that these granules represent particles of absorbed (or "reabsorbed") protein which have been engulfed ("athrocytosed") by the tubular epithelium from the glomerular filtrate.[81–85] Recently there has been some retreat by a few from the still popular point of view that " . . . the droplets are most certainly not a transformation of the cytoplasm of the cell . . . "[86] until now the position is held by one group of workers that the droplets are indeed derived from certain highly specialized cytoplasmic constituents, namely mitochondria, into which the protein of the glomerular filtrate is actively and specifically incorporated.[87] It is further postulated that "the mitochondrial rodlets of the absorbing cells dissolve, liberate their substance into the cytological pool, and in this milieu droplets form. . . . "[88] The concept of athrocytosis of hemoglobin appears still to be acceptable to this group although such a process of particulate absorption seems somewhat at odds with their current concept of mitochondrial activity.

The author of this present review, for reasons detailed elsewhere, concluded, as did others before him,[27] that the droplets were actually the familiar cytoplasmic granules indigenous to the proximal tubular epithelium which had been modified in certain ways, probably principally by intracellular changes in osmotic pressure, so as to appear as swollen, brilliantly refractile, eosinophilic granules.[1] This is not at all to suggest that absorbed protein may not become incorporated into the droplets; rather it is to suggest that the primary change is a swelling of the pre-existing cytoplasmic constituents (granules or rodlets), that these originally present granules do not undergo solution and reformation, and that the incorporation of protein into them is as incidental to their characteristic makeup as is the incorporation of absorbed lipids, carbohydrates and, perhaps above all, water. In human kidneys these droplets, which stain positively with the Gram stain and the periodic acid Schiff reagent (PAS), may be seen inconstantly particularly in glomerular amyloidosis, hemoglobinuric nephrosis, membranous glomerulonephritis, disseminated lupus erythematosus, necrotizing nephrosis due to chemicals and malignant nephrosclerosis. Experimentally, they may be observed with such procedures as the administration of foreign or native protein, incomplete clamping of a renal artery, the production of hemoglobinuria or the injection of renin in the presence of an intact hypophysis and adrenal glands. It is immediately apparent from the diversity of the physiologic and morphologic conditions associated with the hyaline droplets that, at the least, a simple linear relationship between the tubular absorption of protein and the development of these droplets does not exist.

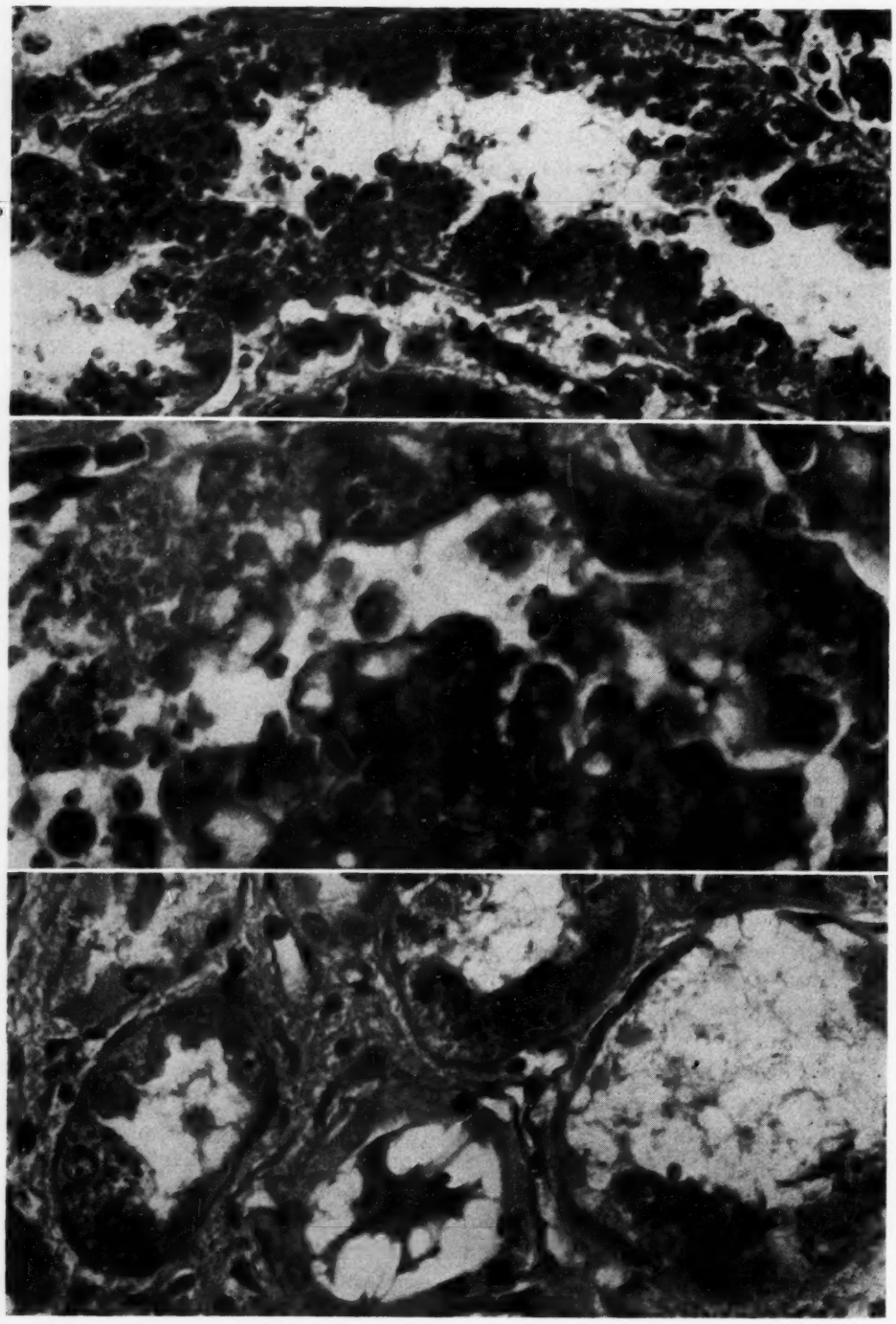

FIG. 36. Hyaline droplets, without hemosiderin, in the epithelium of a proximal convoluted tubule showing their disruption into the tubular lumen. From a human case of hemoglobinuric nephrosis; (hematoxylin and eosin, × 800).

FIG. 37. Hyaline droplets within the parietal epithelium of Bowman's capsule; (hematoxylin and eosin, × 1200).

FIG. 38. Hyaline droplets within the epithelium of proximal convoluted tubules. The cells show various stages of degeneration and regeneration as a consequence of "bursting" of the cells and the disruption of the cytoplasmic droplets into the tubular lumens. From a case of glomerular amyloidosis; (hematoxylin and eosin, × 560).

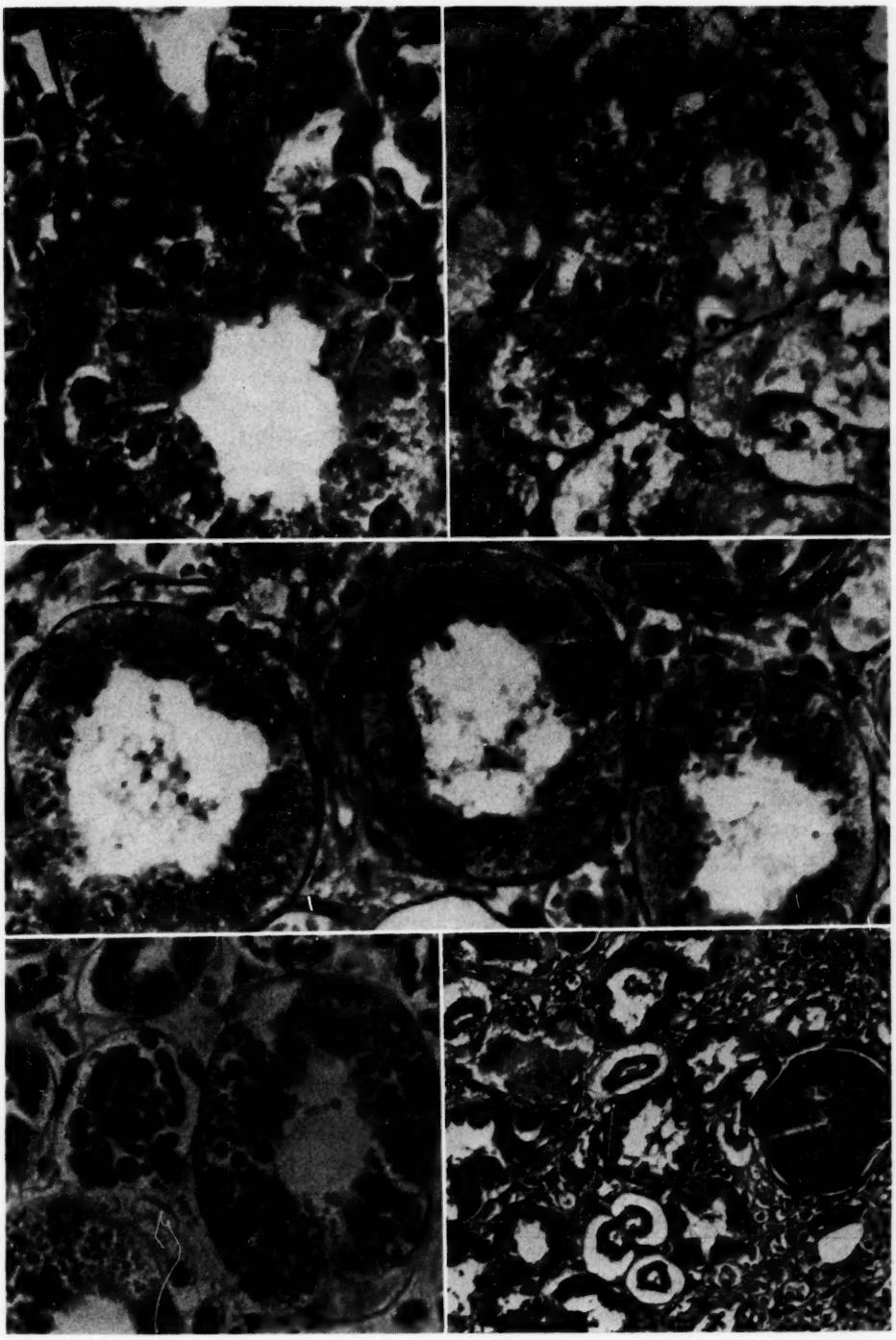

Fig. 39. Hyaline droplets in association with myeloid leukemic infiltration of the kidney and in the absence of proteinuria; (hematoxylin and eosin, × 560).

Fig. 40. Hyaline droplets in the proximal tubular epithelium caused by the intravenous administration of 150 ml. of 50 per cent sucrose solution; (hematoxylin and eosin, × 280).

Fig. 41. Hyaline droplets associated with hemoglobinuric nephrosis (PAS stain after diastase treatment; × 560).

Fig. 42. Hyaline droplets with the Gram stain. It is noted that many of the hyaline droplets are not gram-positive; × 560.

Fig. 43. Myeloma nephrosis from a patient with marked Bence-Jones proteinuria. The inspissated laminated cast typical of the myeloma kidney is noted. Hyaline droplets are not present despite the "dysproteinuria"; (hematoxylin and eosin, × 110).

The resolution of this aspect of the problem of lipid nephrosis acquires importance to the degree that it is assumed, rightly or wrongly, that the tubules contribute to the proteinuria of the nephrotic syndrome through the theoretic mechanism of their failure properly to absorb the protein present in the glomerular filtrate. This suggestion is especially relevant in view of the recently published conclusion, based on observations of dye-stained hyaline droplets, that normally approximately 33 per cent of the circulating plasma protein of the rat is filtered through the glomeruli and thence absorbed by the tubular epithelium where the absorbed protein takes the form of hyaline droplets.[85] If this were the fact—if this much protein were normally filtered and absorbed—then deficient tubules, through their inability to fulfill this presumed function, might very well be in large measure responsible for the excessive proteinuria of lipid nephrosis. However, there is convincing evidence to conclude that the tubules have no significant role in the proteinuria of the nephrotic syndrome.[44,89] The resolution of the problem is important also because of the hypothetic function recently assigned to the hyaline droplets, on the basis principally of their tinctorial reactions, as cellular units specifically concerned with the absorption of and enzymatic activity on amino acids and proteins. This concept also deserves re-examination and in the sections to follow will be considered in some detail.

Evidence against the concept of hyaline droplets representing athrocytosed or absorbed protein: As stated, for several basic reasons it appears more likely that these hyaline granules represent a swelling of the intrinsic, acidophilic cytoplasmic contents—granules and rodlets—of the epithelial cells which existed in their normal unswollen state prior to the appearance of excessive concentration of protein in the glomerular filtrate. In the first place, if the hyaline droplets do in fact represent protein absorbed from tubular lumens, it would appear to be a reasonable enough requirement that direct quantitative relationship between the proteinuria and hyaline droplets be shown to exist. As pathologists and experimentalists in this field[87] have good reason to know, and as the photomicrograph in Figure 11 helps to illustrate, there is no positive correlation between the amount of proteinuria and the concentration of hyaline granules in the renal tubular epithelium of humans with the nephrotic syndrome. The urine of such patients may "boil solid" with protein and yet at autopsy no hyaline granules may be present. Furthermore, there is no positive correlation in lipid nephrosis of whatever etiology between the amount of tubular lipid and hyaline droplets; a much closer correlation exists between tubular lipid and proteinuria. This same lack of correlation between proteinuria and hyaline granules obtains also in instances of poisonings with necrotizing nephrosis, in leukemic infiltrations of the kidney (Fig. 39), at the edge of renal infarcts, in malignant nephrosclerosis, as well as experimentally after partial clamping of a renal artery, and after the injection of hypertonic sucrose, all either in the absence of proteinuria or in association with minute amounts of protein excretion (Figs. 36 and 41).

The fact that hyaline droplets have been observed experimentally following the administration of certain proteins does not negate the foregoing facts, especially in view of the inconstancy of the correlation between the proteinuria and the number of droplets. Moreover, the physiologic proteinuria of normal rats is accompanied either by no hyaline droplets or by no significant numbers of droplets, although contrary statements are in the literature. Even in the case of nephrotoxic nephritis with the nephrotic syndrome, hyaline droplets in the rat kidneys may be sparse. The explanation has been offered that in the instances previously mentioned, as well as in the normal kidneys of rats, hyaline droplets fail to develop because they are "used to" or "are able to handle" the native proteins in contrast with the experimentally administered foreign proteins. As an example to support this vitalistically strained hypothesis the occurrence of hyaline granules with renal amyloidosis is cited. The fact is, of course, that all or the bulk of the proteins excreted in association with nephrotic syndrome due to renal amyloidosis are not foreign proteins and are essentially similar to those excreted as a result of membranous glomerulonephritis. What appears to have been confused with the nature of the native protein in the urine in these instances is the occasional use of foreign proteins in the experimental production of amyloidosis. Contrariwise, Bence-Jones proteinuria frequently occurs in the absence of hyaline droplets and, as a matter of fact, crystals of Bence-Jones protein may be observed in proximal tubular epithelium without droplets; nor were hyaline

droplets described by Baxter and Cotzias[90] in the tubular epithelium of rats made proteinuric with foreign proteins.

Second, hyaline granules, indistinguishable from those under discussion, have been noted following the immersion of slices of kidney in hypotonic solutions.[70,91,92] Presumably these droplets are similar to the swollen mitochondria observed years ago by the Lewises when the cells were subjected to hypotonic solutions. These observations are in harmony with the hypothesis[1] that the hyaline granules represent the effects of altered oncotic relationships between the contents of the tubular lumens and cells, and perhaps interstitial fluid, in which glomerular ischemia may also contribute a role, as will be indicated further. In the nephrotic syndrome such alterations may be contributed to by the oncotic effects of the marked proteinuria, just as, experimentally, hyaline droplets may be produced by hypertonic sucrose. This conclusion is compatible also with the observation that "the number and size of droplets decreased with increasing molecular size of the injected material."[86] As a matter of fact hydropic vacuolization qualitatively similar to that produced with hypertonic sucrose may be present in the cells with the hyaline droplets.[92] To this type of vacuolization the term "osmotic nephrosis" has been applied.[1] Third, study of the morphology of the hyaline granules—their intensely positive reaction to the periodic acid Schiff (PAS) stain, their apparent development from the normal cytoplasmic granules of tubular epithelium with gradual and transitional enlargement from these originally minute granules or rodlets, and the presence, frequently, of the largest granules at the brush border instead of at the base so that they radiate generally in increasing size from the base of the cell to its luminal surface in the kidneys of both humans and animals—all point to their genesis from the cytoplasmic constituents rather than from engulfed material. (Figs. 36 to 42.) This morphologic gradient has prompted the description that "the tubule cells are filled almost to bursting";[86] in point of actual fact there is good reason to believe that when the change is marked the hyaline droplets may indeed burst through into the tubular lumen from the tubular epithelium. (Fig. 36.) This conclusion is supported by the additional, generally disregarded morphologic fact emphasized several years ago, that identical hyaline granules may be observed within the parietal epithelial cells of Bowman's capsule. (Fig. 37.) Surely, the hyaline granules in these cells cannot be attributed to the absorption of protein. The positive PAS stain indicative of a polysaccharide component or coating of these granules has been ascribed to the existence of glycoproteins (or mucoproteins) in egg albumin used for the production of experimental albuminuria. However, it is admitted by the same observers that whereas the percentage of glycoproteins in the egg albumin administered to the experimental animals is high, it is extremely low in the protein in the serum of humans.[84] Notwithstanding this discrepant fact the reaction of the hyaline granules to the PAS stain is equally striking and constant in humans and experimental animals. Fourth, if it were actually true that the hyaline droplets represent, as many believe, merely absorbed protein rather than swollen granules of the intracellular structures, it might be anticipated that, just as tubular hemosiderosis lowers the renal threshold specifically for hemoglobin, so these granules, when abundant, might increase the proteinuria through impeded resorption of protein. As a matter of fact, there is no tendency toward lowering of the albumin clearance in the nephrotic syndrome even at low plasma concentrations of albumin.[44] Smith,[44] as well as Chinard[89] and his associates, conclude that the protein absorptive capacity of the tubules is relatively insignificant in determining the magnitude of proteinuria in the nephrotic syndrome. The load of protein that escapes through the glomerular filter is the determining factor which, in essence, is uninfluenced by the minute amounts absorbed by the tubules. Fifth, perhaps more decisive evidence will be drawn from autoradiographic studies of kidneys from animals to which radioisotopically labelled proteins have been administered. Here, too, the problem of dissociation of the radioactively tagged compound must be rigidly controlled, just as the reversibility of the linkage between dye and protein is to be considered. LeVeen and Fishman[94] have critically discussed and emphasized the limitations of the use of Evans blue (T-1824) as a label in studies of capillary permeability and protein metabolism, especially in view of the fact that the dye forms a dissociable complex with plasma protein. Sixth, it is apparent that in many of the experiments recorded in the literature there has been confusion of hyaline droplets, hemoglobin, hematoidin,

hemosiderin, bile pigments and lipochromes of tubular epithelium. For example, there are citations in the more frequently quoted articles of the identity of "eosinophilic (rather than brown) droplets" with hemoglobin, on the assumption that the presence of hemosiderin in the proximal tubular epithelium is unequivocal evidence that the dissociation of the free, iron-containing molecule from hemoglobin occurred within the cell and that therefore the associated hyaline droplets represented the hemoglobin. In point of fact, whereas the dissociation of hemosiderin from hemoglobin may very well occur within the epithelium, conspicuous hemosiderosis of the tubular epithelium may be observed, as a rule, following protracted hemoglobinuria without evidence of the co-existence of hyaline droplets.[1] Moreover, there appears to be an unwarranted reliance on the stains for hemoglobin as used in paraffin sections of tissue. Morphologists who have used the various modifications of the benzidine reaction for the identification of hemoglobin in sections generally are thoroughly aware of and have often described their undependability. This fact has not always been taken into account nor has the fact that hemin pigment of hemoglobin may dissociate from the globin, especially in an acid medium, and itself color cytoplasmic droplets just as other dyes do, including Evans blue (T-1824).[94]

Furthermore, hyaline droplets within the proximal tubular epithelium of kidneys of patients with hemoglobinuric nephrosis of ten or more days' duration may be as prominent and as strongly positive with PAS stains as in the most protracted and massive proteinuria or with any other renal disease; and this, in spite of complete or almost complete renal shutdown in the hemoglobinuric nephrosis, as well as the absence of hemosiderin in the proximal tubular epithelium. (Fig. 36.) It is suggested that ischemia, particularly glomerular ischemia, plays an important role in the pathogenesis of the hyaline droplets in hemoglobinuric nephrosis. Other supporting evidence of the role of ischemia in the development of hyaline droplets under a great many diverse conditions is the observation of such droplets (1) at the edges of renal infarcts, (2) following the partial experimental occlusion of renal arteries in the absence of infarction, (3) subsequent to the administration of renin, and (4) in malignant nephrosclerosis. Finally, it has been noted that renin administered to rats causes a prompt increase in the normally present proteinuria.[95] The proteinuria is also associated with the occurrence of hyaline droplets in the epithelium of only some of the proximal tubules, as usual, as well as in only some parts of these tubules. The proteinuria has been attributed to either (1) a failure of tubules properly to absorb the protein normally present in the glomerular filtrate of rats, or (2) an increase in intraglomerular pressure resulting from constriction of the efferent glomerular arterioles, a phenomenon produced by renin mediated through angiotonin (hypertensin). In view of the observation that the most striking development of hyaline droplets in the proximal tubular epithelium occurs in patients with malignant nephrosclerosis, and in view of the accepted hypothesis that renin, through its enzymatic production of angiotonin, causes experimental hypertension by constriction of the efferent arterioles,[18] the possibility that ischemia may be the initiating factor in the production of the hyaline droplets in some instances suggests itself. This same mechanism of ischemia might also obtain in membranous and lobular glomerulonephritis, diabetic glomerulosclerosis and glomerular amyloidosis, as well as in nephrosis due to inorganic poisons and even in hemoglobinuric nephrosis. Whether or not the ischemia produces its effects on the cytoplasmic granules through the mediation of intracytoplasmic oncotic changes remains to be determined. Of direct pertinence is the observation of Opie that the osmotic pressure of renal epithelial cells, normally twice that of their surrounding medium, is reduced to approximately the level of that medium after poisoning with bichromate.[92] As mentioned, hyaline droplets are found after poisoning with bichromate, diethylene glycol, uranium nitrate and mercury bichloride.[1,96] The point that is intended for emphasis here is that not only the mitochondria specifically, but all of the cytoplasmic granules, or what Opie[70] prefers to call the "cytochondria," are potential hyaline droplets. It is stated that regenerating tubular cells do not develop hyaline droplets because they lack mitochondria.[86] It should be added that whereas such cells do not develop hyaline droplets in the earlier stages of their regeneration, droplets not only appear prior to their complete maturation and prior to the appearance of basilar rodlets or mitochondria but these droplets are seen first at the luminal side of the cell rather than at its basal aspect.

Special stains and electron microscopic studies: The unreliability of the stains for hemoglobin as used in sections of tissue is just one of a number of hazards in the histochemical analysis of the hyaline droplets. In this era of concentrated attention on histochemistry there is being manifested an increasing susceptibility to the temptation of reading into a histochemical procedure a specificity that either does not exist or is highly dubious. This practice is evident in the chemically specific interpretations of the special stains used for the study of the hyaline droplets. The Gram stain may be mentioned as one of several which have been made the prominent basis of tendentious conclusions. For example, gram-positivity has been attributed to the presence specifically of ribonucleic acid on what is now considered totally inadequate evidence. As Pearse[97] wisely emphasizes, the "insuperable objection to the use of the Gram stain as a histochemical reaction" is the necessity for using differentiation (e.g., by acetone and alcohol). According to Pearse, the only conclusions that can legitimately be drawn from the Gram-positive staining of a structure is "that reactive acid groups are present and that either the constituent molecules are in some way condensed or polymerized, or else a physical barrier such as a lipid or lipoprotein membrane is present." The long-established and well known facts that the pH of a structure and its physical construction—including density, size and coating—are the principal elements of many staining reactions are occasionally subordinated in the zealous search for a specific chemical makeup of cytologic components; this makeup may be prematurely enlisted in the elaboration of a new functional concept.

The principal evidence recited by those who favor the more popular hypothesis of athrocytosis of tubular protein is based on the presence within the epithelium of what is considered to be previously administered dye-labelled protein. The fact that dye itself (e.g., neutral red in perfused Locke's solution with sugar), without apparent linkage to ubiquitous proteins and amino acids, may be productive of stained hyaline epithelial droplets; that tremendous numbers of hyaline droplets may be observed unassociated with proteinuria and, conversely, that massive proteinuria may occur without the formation of hyaline droplets; that the hyaline droplets may be observed in visceral and parietal epithelium of Bowman's capsule, the functions of which obviously do not include the absorption of protein; that the granules may persist in the tubules for weeks, months or even up to a year, so as to be of little use to the body's economy despite its vital need of protein (notwithstanding the conclusion that a third of the plasma protein of rats is daily filtered through the glomeruli and resorbed through the tubules[85]); that dye may dissociate from protein just as dissociation may occur even in a radioactively tagged compound; and that this dissociation of either dye or radioactive element, unless incontrovertibly controlled, may result in gross misinterpretations; and finally the fact that hemosiderin, hemoglobin, lipochrome pigments and the swollen acidophilic droplets of epithelium have frequently been confused with each other or are obviously inadequately identified—all of these facts constitute serious discrepancies in the concept that hyaline droplets are clumps of protein retrieved from tubular lumens. It is no wonder, then, that "when an attempt is made to integrate data into a comprehensive description of proteinuria considerable difficulty is encountered."[87] And, to be sure, some of the foremost proponents of the concept of epithelial athrocytosis of tubular protein, as mentioned, have reversed their position with the hypothesis that the hyaline droplets are really swollen intracellular material—mitochondria—to which an absorbed moiety of protein has been added. That some of the protein present in glomerular filtrates becomes assimilated into these cytoplasmic masses is almost as reasonable as that other substances—lipids and carbohydrates—also become part of these structures. However, this phenomenon is hardly evidence in support of the intraluminal origin of the hyaline droplets as it has been used in the past, nor does it buttress the concept that the mitochondria, to the exclusion of the other cytoplasmic granules, are specifically concerned with the formation of the droplets. It appears more in consonance with the evidence, as herein briefly outlined, that the hyaline droplets, as stated, are derived not merely from the rodlets or mitochondria but from any of the cytoplasmic granules normally present in the proximal tubular epithelium. In view of the characteristic ultrastructure of mitochondria of all cells thus far examined, as manifested particularly by a system of internal ridges (cristae mitochondriales) visible in electron micrographs,[98–100] the mitochondrial nature of hyaline droplets might be indicated if

some residual organelle structure were detectable in these droplets. Apparently, some of the droplets do exhibit traces of such internal ridges or traversing "double membranes;" others do not.[100] Inasmuch as, according to Rhodin,[100] "two distinct types of big granules" other than mitochondria are normally present in the cells of the proximal tubular epithelium, and since these latter structures are normally not at the base where mitochondria reside but at the intermediate cell zone and at the brush border where hyaline droplets tend to form first, it is not clear from the electron microscopic evidence offered why he has not considered the possibility that they, too, may give rise to hyaline droplets.

Functional meaning: Even if, for the sake of the issue under discussion, it were assumed that only the mitochondria were the precursors of hyaline droplets, there remains the problem of whether such structures become swollen because they have absorbed protein and amino acids in the interest of body economy or whether they have become bloated chiefly through the imbibition of water, presumably as a result of changes in oncotic relationships; and, furthermore, that the "bloating," while "physiologic" in most instances, may at times be of such a degree as to damage the original granules or rodlets and, that, if a sufficient number are damaged, the process may actually kill the cell. By no phrase has it been here implied that mitochondria do not have vital functions. What has been suggested is that their mere swelling does not indicate an active absorption of amino acids and protein along with enzymatic metabolism of these substances, as others[87,88] believe. The issue is more than a philologic one because of the important and specific nature of the functions attributed to these hyaline droplets.

While it is true that the appearance of hyaline droplets *in vivo* is usually a completely reversible phenomenon, it is also true that the same phenomenon—involving mitochondria as well as other cytochondria or cytoplasmic granules—is apparently reproducible *in vitro* with non-vital slices of kidney, as Opie[70] has shown. In addition, although the process *in vivo* is, as stated, usually innocuous, the production of hyaline droplets may be so extreme in some of the cells that the droplets do indeed "burst" through the brush border into the tubular lumen. (Fig. 36.) This latter occurrence may be inferred from sections illustrating not only necrotizing nephrosis following potassium dichromate, for example, but also in kidneys which have not been subjected to poisons or excessive proteinuria but in which the formation of hyaline droplets is particularly marked, as already mentioned. In these instances tubular cells may be observed with numerous and huge hyaline droplets, some of which have disrupted the brush border and extruded into the lumen. (Fig. 36.) These are not observations of artefact. Not only may hyaline droplets be found also in the urine but evidence of regeneration of adjacent tubular cells is commonly noted. (Fig. 38.) Therefore, whether or not the process responsible for the appearance of hyaline droplets is harmless to cells, as it most often is, depends on the degree of the process, or, to borrow Shannon's phrase and thought on this subject,[101] on the degree to which the "normal economy of the cell" is changed. To cite a closely analogous situation, whether or not a cell immersed in a hypotonic solution bursts or simply swells depends on the tonicity of the milieu and the duration of exposure. In other words, vitality of a cell is not essential for the production of hyaline droplets, and, secondly, in some instances the hyaline droplets may be extruded into the tubular lumen and be associated with cellular damage or necrosis. To state it still another way, the hyaline droplets are regarded as a manifestation of a biophysical strain—due probably to ischemia and changes in local oncotic relationships—to which the individual cell is most often physically able to readjust but which occasionally is too severe to be survived.

SUMMARY AND CONCLUSIONS

1. The nephrotic syndrome, "pure" or "mixed," is associated with one of the following lesions: (1) membranous glomerulonephritis, (2) lobular glomerulonephritis, (3) diabetic glomerulosclerosis, (4) glomerular amyloidosis, and (5) bilateral renal vein thrombosis.

2. It is suggested that in all instances of the nephrotic syndrome, the rare instance of that due to renal vein thrombosis possibly excepted, one of the foregoing types of glomerular lesions is present and is the basis for the proteinuria which is the engine to the train of signs and symptoms known as the nephrotic syndrome.

3. The renal lesion responsible for "lipid nephrosis" of children as well as adults, or the so-called "nephrotic phase of glomerulonephritis," is either diffuse membranous or lobular

glomerulonephritis: the former is the more common, particularly among children.

4. The clinically "pure" form of the nephrotic syndrome is most likely to be associated with membranous glomerulonephritis; the "mixed" type (i.e., the nephrotic syndrome plus hypertension, hematuria, moderate amounts of pyuria, and azotemia) is associated with either membranous or lobular glomerulonephritis or, of course, diabetic glomerulosclerosis or glomerular amyloidosis.

5. Membranous glomerulonephritis is the same lesion that occurs in a variety of infections including the treponematoses and malaria, toxemias of pregnancy, disseminated lupus erythematosus and reactions to allergic dermatoses and to many drugs. Acute membranous glomerulonephritis is a relatively common finding in postmortem material, although there are impressions to the contrary.

6. Membranous glomerulonephritis either regresses completely, or, in time and with progressive sclerosis, evolves as lobular glomerulonephritis or sclerosing glomerulonephritis ("secondarily contracted kidney"). In the sclerotic stage the kidneys are granular and shrunken, as in the late end-stage of acute hemorrhagic ("type I") glomerulonephritis and the nephrotic syndrome becomes replaced by compensatory polyuria with urine of low specific gravity, diminution of proteinuria with loss of edema, and finally renal insufficiency with uremia.

7. The designations "pure" and "mixed" lipid nephrosis of both children and adults are arbitrary segregations and do not indicate fundamental etiologic or morphologic differences but rather the degree to which the glomerular capillary lumens are encroached upon, the severity of the changes in basement membranes, the superimposed exudative, proliferative and sclerotic reactions and other morphologic phenomena. Similarly, the disparities in the clearance studies conducted in different individuals or in the same individual at different times is determined by corresponding definitive, dynamic rather than static, morphologic changes which obviously alter glomerular blood flow and filtration as well as tubular activity.

8. Because of the integrity of glomerular architecture and the apparent reversibility of the lesions of membranous glomerulonephritis, this form of "lipid nephrosis" would appear most susceptible to the beneficial effects of ACTH and cortisone as well as other therapeutic modalities. It is noted, conversely, that the very agents which are therapeutically effective, (e.g., cortisone and nitrogen mustards) may in some instances have an adverse or even fatal effect inherent in their capacity for biphasic action. This same type of dual response may be caused also by certain infections, including even malaria.

9. The pathogenesis and significance of the renal tubular changes in the nephrotic syndrome are analyzed.

10. It is concluded that hyaline droplets are not formed by athrocytosis and that their occurrence and conspicuousness are not necessarily related to the degree of proteinuria, the presence of abnormal proteins, or even the occurrence of proteinuria.

11. It is also concluded that, although mitochondria may have vital biochemical functions, the hyaline droplets not only do not reflect the performance of these functions (e.g., absorption and enzymatic metabolism of amino acids and proteins) but, rather, the hydropic swelling characteristic of hyaline droplets is indicative of a physical disturbance of the cytoplasmic contents—granules and rodlets—probably related to ischemia and osmotic changes, usually mild and reversible but at times severe and destructive.

12. Finally, it is stressed that a great deal of the potential information to be derived from meticulous biochemical studies conducted in patients with the nephrotic syndrome is lost because of the frequency with which they are paralleled with relatively meaningless histologic diagnoses such as "chronic nephritis"; as well as "normal kidneys" by observers who, in fact, have inadequately evaluated the lesions, particularly of membranous glomerulonephritis.

REFERENCES

1. Allen, A. C. The Kidney—Medical and Surgical Diseases. New York, 1951. Grune and Stratton, Inc.
2. Ellis, A. Natural history of Bright's disease; clinical, histological and experimental observations. *Lancet*, 1: 1, 1942.
3. Ehrich, W. E., Forman, C. W. and Seifer, J. Diffuse glomerular nephritis and lipid nephrosis. Correlation of clinical, morphological and experimental observations. *Arch. Path.*, 54: 463, 1952.
4. Fishberg, A. M. Hypertension and Nephritis, 5th ed. Philadelphia, 1954. Lea and Febiger.
5. Munk, F. Pathologie und Klinik der Nierenerkrankungen (Nephrosen, Nephritiden and

Schrumpfnieren), 2nd ed. Berlin and Vienna, 1925. Urbach and Schwarzenberg.

6. Allen, A. C. and Spitz, S. Comparative study of the pathology of scrub typhus (tsutsugamushi disease) and other rickettsial diseases. *Am. J. Path.*, 21: 603, 1945.
7. Spitz, S. The pathology of acute falciparum malaria. *Mil. Surgeon*, 99: 555, 1946.
8. Fahr, T. Die patholgisch-anatomischen Veränderungen der Niere und Leber bei der Eklampsie. In: Die Eklampsie. Edited by H. Hinselmann. Bonn, 1924. F. Cohen.
9. Bell, E. T. Renal Disease, 2nd ed. Philadelphia, 1950. Lea & Febiger.
10. Rytand, D. A. Fatal anuria, nephrotic syndrome, and glomerulonephritis as sequels of dermatitis of poison oak. *Am. J. Med.*, 5: 548, 1948.
11. Ehrenreich, T. and Olmstead, E. V. Malignant hypertension following the administration of cortisone in periarteritis nodosa. *Arch. Path.*, 52: 145, 1951.
12. Derow, H., Schlesinger, M. J. and Savitz, H. A. Chronic progressive occlusion of the inferior vena cava and the renal and portal veins with clinical picture of nephrotic syndrome. *Arch. Int. Med.*, 63: 626, 1939.
13. Siegal, S. and Allen, A. C. Intercapillary glomerulosclerosis (Kimmelstiel-Wilson) and the nephrotic syndrome in diabetes mellitus. *Am. J. M. Sc.*, 201: 516, 1941.
14. Kimmelstiel, P. and Wilson, C. Intercapillary lesions in the glomeruli of the kidney. *Am. J. Path.*, 12: 83, 1936.
15. Allen, A. C. So-called intercapillary glomerulosclerosis—a lesion associated with diabetes mellitus: morphogenesis and significance. *Arch. Path.*, 32: 33, 1941.
16. Hall, B. V. Studies of normal glomerular structure by electron microscopy. Proc. Fifth Annual Conference on the Nephrotic Syndrome, p. 1–24. New York, 1953, National Nephrosis Foundation.

16a. Rifkin, H., Leiter, L. and Berkman, J. Diabetic Glomerulosclerosis. The Specific Renal Disease of Diabetes Mellitus. Springfield, Ill., 1952. Charles C Thomas.

17. Pappenheimer, J. R. Passage of molecules through capillary walls. *Physiol. Rev.*, 33: 387, 1953.
18. Goldring, W. and Chasis, H. Hypertension and Hypertensive Disease. New York, 1944. The Commonwealth Fund.
19. Rich, A. R., Bennett, I. L., Cochran, T. H., Griffith, P. C. and McGoon, D. C. Effect of ACTH and cortisone upon experimental anaphylactic glomerulonephritis. *Bull. Johns Hopkins Hosp.*, 88: 189, 1951.
20. Addis, T. Glomerular Nephritis. Diagnosis and Treatment. New York, 1948. The Macmillan Co.
21. Zuelzer, W. W., Palmer, H. D. and Newton, W. A., Jr. Unusual glomerulonephritis in young children, probably radiation nephritis. *Am. J. Path.*, 26: 1019, 1950.
22. Vallery-Radot, P., Maurice, G., Wolfromm, R. and Guiot, G. Nephrose lipoidique secondaire à un traitement aurique. *Bull. et mém. Soc. d. méd. hôp. de Paris*, 58: 96, 1942.
23. Barnett, H. L., Simons, D. J. and Wells, R. E. Nephrotic syndrome occurring during tridione therapy. *Am. J. Med.*, 4: 760, 1948.
24. Allen, A. C. and Sirota, J. H. Morphogenesis and significance of degenerative verrucal endocardiosis (terminal endocarditis, endocarditis simplex, nonbacterial thrombotic endocarditis). *Am. J. Path.*, 20: 1025, 1944.
25. Cabot Case 38052. *New England J. Med.*, 246: 193–198, 1952.
26. Barness, L. A., Moll, G. H. and Janeway, C. A. Nephrotic syndrome. I. Natural history of the disease. *Pediatrics*, 5: 486, 1950.
27. Volhard, F. and Fahr, T. H. Die Brightische Nierenkrankheit; Klinik, Pathologie und Atlas. Berlin, 1914. J. Springer.
28. Fahr, G. E. Mechanism of hypertension in chronic genuine nephrosis. In: Hypertension—A Symposium. Edited by E. T. Bell. Minneapolis, 1951. Univ. Minnesota Press.
29. Luetscher, J. A., Deming, Q. B. and Piel, C. F. Advances in the management of the nephrotic state. *J. A. M. A.*, 153: 1236, 1953.
30. Schwarz, H., Kohn, J. L. and Weiner, S. B. Lipoid nephrosis, observations over a period of 20 years. *Am. J. Dis. Child.*, 65: 355, 1943.
31. Bell, E. T. Glomerular lesions associated with endocarditis. *Am. J. Path.*, 8: 639, 1932.
32. Cafferena, F. M. Pathologisch-anatomische Beteiligung der Nieren beim Fleckfieber. *Zentralbl. f. allg. Path. u. path. Anat.*, 67: 203, 1937.
33. Wolbach, S. B., Todd, J. L. and Palfrey, F. W. The Etiology and Pathology of Typhus. Cambridge, 1922. Harvard University Press.
34. Heymann, W. and Lund, H. Z. Nephrotic syndrome in rats. *Pediatrics*, 7: 691, 1951.
35. Heymann, W. and Hackel, D. B. Early development of anatomic and blood changes in the nephrotic syndrome in rats. *J. Lab. & Clin. Med.*, 39: 429, 1952.
36. Oeding, P. Serological studies in rheumatoid arthritis and other rheumatic diseases. Universitetet I. Bergen Arbok. 1952–3. Medisinsk rekke Nr. 1.
37. Fischel, E. E. and Gajdusek, D. C. Serum complement in acute glomerulonephritis and other renal diseases. *Am. J. Med.*, 12: 190, 1952.
38. Kellett, C. E. Complement titre in acute nephritis with special reference to causation by reversed anaphylaxis. *Lancet*, 1: 1262, 1936.
39. Lange, K., Strang, R. and Slobody, L. B. Significance of serum complement levels for diagnosis and prognosis of acute and subacute glomerulonephritis. *Bull. New York Acad. Med.*, 30: 315, 1954.
40. Bell, E. T. Renal lesions in toxemias of pregnancy. *Am. J. Path.*, 8: 1, 1942.
41. Sheehan, H. L. Pathologic lesions in hypertensive toxemias of pregnancy. In: Toxemias of Pregnancy, Human and Veterinary. Edited by J. Hammond et al. Ciba Foundation Symposium. Philadelphia, 1950. Blakiston Co.
42. Emerson, K., Jr., Futcher, P. H. and Farr, L. E. The relation of high and low urea clearances to the inulin and creatinine clearances in children with the nephrotic syndrome. *J. Clin. Investigation*, 20: 361, 1941.

43. Lauson, H. D., Forman, C. W., McNamara, H., Mattar, G. and Barnett, H. L. The effect of corticotropin (ACTH) on glomerular permeability to albumin in children with the nephrotic syndrome. *J. Clin. Investigation*, 33: 657, 1954.
44. Smith, H. W. The Kidney. Structure and Function in Health and Disease. New York, 1951. Oxford University Press.
45. Bruck, E., Rapoport, M. and Rubin, M. I. Renal functions in course of the nephrotic syndrome in children. *J. Clin. Investigation*, 33: 699, 1954.
46. Armstrong, S. H., Jr., Kark, R. M., Schoenberger, J. A., Shatkin, J. and Sights, R. Colloid osmotic pressure of serum proteins in nephrosis and cirrhosis: relations to electrophoretic distributions and average molecular weights. *J. Clin. Investigation*, 33: 297, 1954.
47. Keys, A., Taylor, H. L., Mickelsen, O. and Henschel, A. Famine edema and mechanism of its formation. *Science*, 103: 669, 1946.
48. Baez, S., Mazur, A. and Shorr, E. Hepatorenal factors in circulatory homeostasis. xx. Antidiuretic action of hepatic vasodepressor VDM (ferritin). *Am. J. Physiol.*, 162: 198, 1950.
49. Eder, H. A., Lauson, H. D., Chinard, F. P., Grief, R. L., Cotzias, G. C. and Van Slyke, D. D. Study of mechanisms of edema formation in patients with the nephrotic syndrome. *J. Clin. Investigation*, 33: 636, 1954.
50. Metcoff, J., Nobuyuki, N. and Rance, C. P. On the role of the kidney during nephrotic edema: potassium excretion and sodium retention. *J. Clin. Investigation*, 33: 665, 1954.
51. Robinson, F. H., Jr. and Farr, L. E. Relation between clinical edema and the excretion of antidiuretic substance in urine. *Ann. Int. Med.*, 14: 42, 1940.
52. Chasis, H., Goldring, W. and Baldwin, D. S. Effect of febrile plasma, typhoid vaccine and nitrogen mustard on renal manifestations of human glomerulonephritis. *Proc. Soc. Exper. Biol. & Med.*, 71: 563, 1949.
53. Rosenman, R. H., Solomon, B., Byers, S. and Friedman, M. Arresting effect of heparin upon experimental nephrosis of rats. *Proc. Soc. Exper. Biol. & Med.*, 86: 599, 1954.
54. Kramár, J. Endocrine regulation of capillary resistance. *Science*, 119: 790, 1954.
55. Schwab, L., Moll, F. C., Hall, T., Bean, H., Kirk, M., Hawn, C. V. Z. and Janeway, C. A. Experimental hypersensitivity in the rabbit. Effect of inhibition of antibody formation by x-radiation and nitrogen mustards on histologic and serologic sequences and on behavior of serum complement following single large injections of foreign proteins. *J. Exper. Med.*, 91: 505, 1950.
56. Long, J. B. and Favour, C. B. Ability of ACTH and cortisone to alter delayed type bacterial sensitivity. *Bull. Johns Hopkins Hosp.*, 87: 186, 1950.
57. Rich, A. R., Berthrong, M. and Bennett, I. L., Jr. The effect of cortisone upon the experimental cardiovascular and renal lesions produced by anaphylactic hypersensitivity. *Bull. Johns Hopkins Hosp.*, 87: 549, 1950.
58. Carey, R. A., Harvey, A. M. and Harvard, J. E. Effect of adrenocorticotropic hormone (ACTH) and cortisone on the course of disseminated lupus erythematosus and periarteritis nodosa. *Bull. Johns Hopkins Hosp.*, 87: 424, 1950.
59. Davis, R. A. and Riley, C. M. Serum complement levels in the nephrotic syndrome. *Am. J. Dis. Child.*, 86: 640, 1953.
60. Adlersberg, D., Schaeffer, L. and Drachman, S. R. Development of hypercholesterolemia during cortisone and ACTH therapy. *J. A. M. A.*, 144: 909, 1950.
61. Gordon, D., Kobernick, S. D., McMillan, G. C. and Duff, G. L. Effect of cortisone on serum lipids and on the development of experimental cholesterol atherosclerosis in the rabbit. *J. Exper. Med.*, 99: 371, 1954.
62. Hertzstein, J., Chun-i, W. and Adlersberg, D. Effect of heparin on plasma lipid partition in man: studies in normal persons and in patients with coronary atherosclerosis, nephrosis, and primary hyperlipemia. *Ann. Int. Med.*, 40: 290, 1954.
63. Stavitsky, A. B., Hackel, D. B. and Heymann, W. Reduction of serum complement following *in vivo* tissue antigen—antibody reactions. *Proc. Soc. Exper. Biol. & Med.*, 85: 593, 1953.
64. Good, R. A. and Thomas, L. Studies on the generalized Shwartzman reaction. iv. Prevention of the local and generalized Shwartzman reactions with heparin. *J. Exper. Med.*, 97: 871, 1953.
65. Nikkilä, E. Studies on lipid-protein relationships in normal and pathological sera and effect of heparin on serum lipoprotein. *Scandinav. J. Clin. & Lab. Invest.*, 5: suppl. 8, p. 1, 1953.
66. Rennie, J. B. Edematous syndrome of nephritis with special reference to prognosis. *Quart. J. Med.*, 16: 21, 1947.
67. Metcoff, J., Rance, C. P., Kelsey, W. M., Nakasone, N. and Janeway, C. A. Adrenocorticotrophic hormone (ACTH) therapy of the nephrotic syndrome in children. *Pediatrics*, 10: 543, 1952.
68. Heymann, W. and Clark, E. C. Pathogenesis of nephrotic hyperlipemia. *Am. J. Dis. Child.*, 70: 74, 1945.
69. Boyd, E. M. Species variation in normal plasma lipids estimated by oxidative micromethods. *J. Biol. Chem.*, 143: 131, 1942.
70. Opie, E. L. Cytochondria of normal cells, of tumor cells and of cells with various injuries. *J. Exper. Med.*, 86: 45, 1947.
71. Lewis, M. R. and Lewis, W. H. Mitochondria (and other cytoplasmic structures) in tissue cultures. *Am. J. Anat.*, 17: 339, 1914–15.
72. Fried, C. T. and Henley, W. Deficiency in gamma globulin with edema and hypoproteinemia. *Pediatrics*, 14: 59, 1954.
73. Strisower, B., Gofman, J. W., Galioni, E. F., Alamada, A. A. and Simon, A. Effect of thyroid extract on serum lipoporteins and serum cholesterol. *Metabolism*, 3: 218, 1954.
74. Regant, L. and Riggs, D. S. Thyroid function in nephrosis. *J. Clin. Investigation*, 31: 789, 1952.
75. Earlaw, M. S. S. and Bolliger, A. Experimental renal disease produced by x-ray. *J. Path. & Bact.*, 34: 603, 1931.

76. Johnson, G. C., Bauer, F. C., Jr., Hrisch, E. F. and Carbonaro, L. Lipemia of rabbits following unilateral occlusion of renal vessels. *Arch. Path.*, 52: 115, 1951.
77. Bauer, F. C., Jr., Hirsch, E. F., Carbonaro, L. and Johnson, G. C. Potassium dichromate poisoning and repeated poisoning with uranyl nitrate. Effect on serum lipids of rabbits. *Arch. Path.*, 56: 135, 1953.
78. Blix, G. Electrophoresis of lipid-free blood serum. *J. Biol. Chem.*, 134: 495, 1941.
79. Russ, E., Eder, H. A. and Barr, D. P. Protein–lipid relationships in human plasma. I. In normal individuals. *Am. J. Med.*, 11: 468, 1951.
80. Terbrüggen, A. Über das Vorkommen hyaliner Tropfen in der Niere in Abhängigkeit vom Auftreten körperfremden Eiweiss. *Beitr. path. Anat.*, 86: 235, 1931.
81. Gérard, P. and Cordier, R. Esquisse d'une histophysiologie comparée du rein des vertébrès. *Biol. Rev.*, 9: 110, 1934.
82. Smetana, H. and Johnson, F. R. Origin of colloid and lipoid droplets in epithelial cells of renal tubules. *Am. J. Path.*, 18: 1029, 1942.
83. Rather, L. J. Filtration, resorption, and excretion of protein by the kidney. *Medicine*, 31: 357, 1952.
84. Davies, J. Cytologic evidence of protein absorption in fetal and adult mammalian kidneys. *Am. J. Anat.*, 94: 45, 1954.
85. Sellers, A. L., Griggs, N., Marmorston, J. and Goodman, H. C. Filtration and reabsorption of protein by the kidney. *J. Exper. Med.*, 100: 1, 1954.
86. Oliver, J. Structure of metabolic process in nephron. *J. Mt. Sinai Hosp.*, 15: 175, 1948–49.
87. Oliver, J., MacDowell, M. and Lee, Y. C. Cellular mechanisms of protein metabolism in the nephron. I. Structural aspects of proteinuria; tubular absorption, droplet formation and the disposal of proteins. *J. Exper. Med.*, 99: 589, 1954.
88. Lee, Y. C. Cellular mechanism of protein metabolism in the nephron. III. Histochemical characteristics of amino acid droplets. *J. Exper. Med.*, 99: 621, 1954.
89. Chinard, F. P., Lauson, H. D., Eder, H. A., Grief, R. L. and Heller, A. Study of the mechanism of proteinuria in patients with the nephrotic syndrome. *J. Clin. Investigation*, 33: 621, 1954.
90. Baxter, J. H. and Cotzias, G. C. Effects of proteinuria on kidney. Proteinuria, renal enlargement and renal injury consequent on protein solutions in rats. *J. Exper. Med.*, 89: 643, 1949.
91. Opie, E. L. Osmotic system within the cytoplasm of cells. *J. Exper. Med.*, 87: 425, 1948.
92. Opie, E. L. Effect of injury by toxic agents upon osmotic pressure maintained by cells of liver and of kidney. *J. Exper. Med.*, 91: 285, 1950.
93. Laas, E. Die hyalinen Tropfen in der Niere. *Virchow's Arch. f. path. Anat.*, 286: 426, 1932.
94. Le Veen, H. H. and Fishman, W. H. Combination of Evans blue with plasma protein; its significance with plasma protein in capillary permeability studies, blood dye disappearance curves and its use as a protein tag. *Am. J. Physiol.*, 151: 26, 1947.
95. Addis, T., Barrett, E. Boyd, R. I. and Ureen, H. Renin proteinuria and pressor effect of renin. *J. Exper. Med.*, 89: 131, 1949.
96. Hunter, W. C. and Roberts, J. M. Glomerular changes in kidneys of rabbits and monkeys induced by uranium nitrate, mercuric chloride and potassium bichromate. *Am. J. Path.*, 8: 665, 1932.
97. Pearse, A. G. E. Histochemistry. Theoretical and Applied. Boston, 1953. Little, Brown & Co.
98. Palade, G. E. The fine structure of mitochondria. *Anat. Rev.*, 114: 427, 1952.
99. Palade, G. E. An electron microscopic study of the mitochondrial structure. *J. Histochem. & Cytochem.*, 1: 188, 1953.
100. Rhodin, J. Correlation of ultrastructural organization and function in normal and experimentally changed proximal convoluted tubule cells of the mouse kidney. Stockholm, 1954. Godvil.
101. Shannon, J. A. Renal Function. Transactions of the First Conference. Edited by S. E. Bradley, New York, 1949. Josiah Macy Jr. Foundation.

Seminars on the Hemolytic Anemias

Hemolytic Anemia*

Direct and Indirect Indications, Pathogenetic Mechanisms and Classifications

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THE separation of hemoglobin from the effete red cell (hemolysis) is a normal process affecting approximately 1 per cent of the red cells in the circulation every day. If the life span of the red cells, normally about 120 days, is reduced, and hemolysis thereby increased, anemia may or may not result. In the presence of extraordinarily severe hemolysis, when the life span of the red cell is reduced to a matter of a few days, the normal productive capacity of the marrow is insufficient to keep pace with the hemolytic process and anemia ensues. If, on the other hand, blood destruction is only two or four or even six times normal, the bone marrow may compensate by increased blood production and in sufficient degree to prevent anemia from developing. Thus one may distinguish, as Crosby[1] has suggested, between *compensated* and *decompensated* hemolytic anemia. In any event, whether compensated or decompensated, various indications of increased hemolysis, both direct and indirect, are always present. By "direct," we mean the direct consequences of the breakdown of red blood cells; by "indirect," the secondary effects which develop.

INDICATIONS OF INCREASED HEMOLYSIS

Direct	Indirect
*Diminished red cell survival time	
Hemoglobinemia	Bone marrow hyperplasia
Hemoglobinuria (only if renal threshold for hemoglobin is exceeded)	Erythropoiesis markedly hyperactive
Hemosiderinuria	
Icterus: bilirubinemia ("indirect" type)	
Increased urinary urobilinogen	*Reticulocytosis (above 5%)
*Increased fecal urobilinogen	
Anemia (if capacity of bone marrow is exceeded)	Leukocytosis
*Spherocytosis	Polymorphonuclear increase
Increased hypotonic fragility	
Splenomegaly	Thrombocytosis
	Splenomegaly

* Most important "landmarks" of increased hemolysis.

A diminished red cell survival time is the central feature and, in fact, synonymous with hemolytic disease. When the survival time is normal, the degree of hemolysis is normal; when the red cell life span becomes decreased, various indications of increased hemolysis are present. The measurement of the life span of the patient's red cells may be performed either by injecting some of the patient's red cells into a normal person's circulation and observing how long it takes them to disappear; or by tagging some of

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the patient's (removed) red cells with a radioactive material such as chromate, reinjecting them, and observing the progressive decay of radioactivity.[2] The first method is often very difficult because (1) the patient is usually quite anemic to give blood for transfusion and (2) the patient's blood must be compatible yet dissimilar from that of the transfused normal (Ashby survival time technic).[3] This involves the use of high titer antisera. Most red cell survival time estimations have been made by transferring normal compatible but type-dissimilar red cells into the patient's circulation and counting their number from day to day. If the survival time of the transfused cells is normal, the hemolytic fault is said to be an "intrinsic" one; if short, "extrinsic," i.e., due to extraneous factors acting upon the transfused red cells.[4] The use of radioactive chromate for determination of the patient's own red cell life span may well replace determinations by the methods previously used.

Normally, and even under conditions of greatly increased blood breakdown, hemolysis appears to take place largely through cellular (reticulo-endothelial) pathways, with the eventual production of increased amounts of bile pigment. Despite rapid blood destruction, the plasma hemoglobin level rarely exceeds 5 mg. per 100 cc. Under certain special circumstances, however, the red cells may undergo "explosive" and "direct" destruction within the circulation, apparently without the mediation of the reticulo-endothelial system or the spleen. The degree of hemoglobinemia which then ensues is naturally dependent upon the number of red cells hemolyzed; if the concentration of hemoglobin in the plasma is increased to levels above 100 to 150 mg., hemoglobin spills over into the urine. Even in the absence of hemoglobinuria, however, well defined *hemosiderinuria* occurs when the plasma hemoglobin level exceeds 20 mg. per 100 cc.[5] It should be noted that hemoglobinemia, even when only slightly above the normal value of 5 mg. per 100 cc., provides unequivocal evidence of increased hemolysis, and may thus be an excellent indicator of hemolytic disease.[5]

In the presence of increased hemolysis the serum bilirubin usually increases to levels above 1.0 mg. per 100 cc., and is of the "indirect" variety. Bilirubinemia up to levels of 2 to 5 mg. is by no means invariably present, since the passage of bilirubin through the liver, particularly in childhood, may be so rapid as to cause no appreciable rise in the total serum bilirubin. Nevertheless, the output of bile pigment in the intestinal tract is invariably increased and, with certain rare exceptions (e.g., "heme diversion" in pernicious anemia[6]), an increase in the daily fecal urobilinogen output is indicative of increased hemolysis.[7] That the daily fecal urobilinogen value can be taken as an *exact* measurement of hemolysis is, however, open to considerable question. What is measured as fecal "urobilinogen" is a complex of various pigments, probably derived to some extent from sources other than hemoglobin. Despite the numerous imperfections and inadequacies of the method, it still has real value as a good indicator of the degree of hemolysis.[8]

It is well to remember that the amount of urobilinogen in the feces must be equated with (1) the hemoglobin value and (2) the body weight. Thus the expected daily output of urobilinogen in a five year old child with an anemia of 5 gm. per 100 cc. is hardly to be compared with that of an adult male having 10 gm. of hemoglobin per 100 cc. A rough method of computation is to utilize the formula,* which takes into account the hemoglobin reading and weight (and thus roughly the red cell mass) of the patient.

Thus a five year old child weighing 20 kg., with 5 gm. of hemoglobin per 100 cc., is found to have a fecal urobilinogen output of 50 mg. per day. To compare this with the normal output it is necessary in this example to multiply by 3 for the low hemoglobin value and by 3.5 for the weight, i.e., by approximately 10 for the determined urobilinogen value. This would change the actual figure of 50 mg. to approximately 500 mg., a high value indicative of increased hemolysis. A somewhat more accurate measurement is provided by the *hemolytic index*,[8] determined by the following formula:

$$\frac{\text{* Normal hemoglobin (approximately 15 gm.) in gm. per 100 cc.}}{\text{Gm. of hemoglobin/100 cc. in patient}} \times \frac{\text{Normal adult weight (approximately 70 kg.)}}{\text{Patient's weight}} \times \text{Daily fecal urobilinogen output (mg.)} =$$

Corrected (estimated) daily fecal urobilinogen output in mg.

$$\frac{\text{Mg. of fecal urobilinogen output per day (average of 4-day stool collection)}}{\text{Total hemoglobin in gm. (determined from knowledge of the hemoglobin and the red cell volume)}} \times 100$$

This index expresses the urobilinogen excretion per day in relationship to 100 gm. of hemoglobin. The normal value is 11 to 21.

The urinary urobilinogen value is almost always increased in hemolytic disease, giving the urine a peculiar brownish-orange color. However, an absolute increase in urinary urobilinogen does not have nearly the significance of an increase in the fecal pigment, since to a large extent the amount of urinary pigment is dependent upon the functional capacity of the liver. Nevertheless, in the presence of a well functioning liver the course of hemolysis in a given case can be followed to some extent by performing quantitative determinations of the urinary urobilinogen.

In the newborn and in early infancy, fecal urobilinogen determinations are of but little value because the bacterial flora of the intestines has not yet been established, with the result that bilirubin and not urobilinogen is excreted.[9] A somewhat similar situation occurs when various broad-spectrum antibiotics such as aureomycin are administered with the result that the intestinal tract is sterilized. Under such circumstances the bilirubin of the bile is not converted to urobilinogen, with resultant very low values in the feces. At least in hemolytic disease of the newborn (erythroblastosis fetalis), the course of the hemolytic disease can be followed by quantitative bilirubin estimations of the feces.[10]

Examination of a well spread and well stained blood smear will reveal the presence or absence of *spherocytosis*. Spherocytes are small, round, thick, densely staining red cells which appear to have a somewhat brownish color as compared to the normal, pink-staining red cell. There is no central clear zone as in the normal biconcave disc. When spherocytes occur simultaneously with the much larger polychromatophilic reticulocytes (v. seq.), the red cell diameter population presents a "biphasic" or double-peaked curve.[11] Increased *hypotonic fragility* may or may not be present in a given case of hemolytic disease. When present, it indicates the presence of spherocytosis and is in reality another indirect method for the measurement of this phenomenon. Many cases of hemolytic anemia have normal or even decreased hypotonic fragility, so too much reliance must not be placed on this point. When the hypotonic fragility test is charted to record the hemolytic increments from one hypotonic solution to the next one,[12] a graphic "thickness population" curve is set up which shows at a glance a shift to a thick or thin red cell population, biphasic or multiphasic types of red cell thickness, the percentage of red cells that are hemolyzed in the various solutions, and thus their thickness, etc. This method is of particular importance in studying Mediterranean anemia which has a characteristic "shift to the right," i.e., increased resistance and a multiphasic type of red cell thickness population.

Probably the best single "signpost," however, of hemolytic anemia is the finding of a well defined reticulocytosis of 5 per cent or over. Although by no means specific for the disorder, this finding should make one suspect it, and then to try to find confirmation or negation by other tests. In a well marked case of hemolytic anemia other indications of increased regenerative activity of the bone marrow are present, including leukocytosis, increased polymorphonuclears with increased band forms, increased platelets, and at times nucleated red cells. The bone marrow itself shows a striking increase in erythropoietic cells, which stand out against the other cellular constituents of the marrow. It is well to remember that at times the "indirect" indications of hemolytic disease(reticulocytosis and the like) are more prominent than such direct indications as jaundice, bilirubinemia, etc. Also, that *all* the various indications of increased hemolysis are hardly ever present together in a given case, although at least one and usually two or three determining features are always found.

Splenomegaly is often but not invariably present in hemolytic anemia. It may be directly connected with the hemolytic state and in fact largely responsible for it, or it may be the end result of the increased work-load upon the spleen consequent to increased hemolysis. Absence of palpable splenomegaly does not necessarily rule out enlargement of the spleen, which may occupy a transverse position under the diaphragm or even be kept from enlarging downward by adhesions between the diaphragm and splenic capsule. Careful spot x-ray examinations may disclose splenomegaly in the absence of palpable enlargement.

PATHOGENETIC MECHANISMS

Hemolytic anemia is fundamentally a reflection of diminished red cell survival time. The normal red cell in the circulation has a finite life span of approximately 120 days from the time of its emission from the bone marrow until its eventual destruction. In hemolytic anemia, the red cell may last for a day or for eighty days; in any event, its life span is shorter than normal.

Very little is known of the manner in which the normal red cell dies or is destroyed. We know it is produced in the bone marrow, where it is denucleated; we know that it makes its way into the blood stream, still containing a few evidences of its youth (reticulated material, relatively high metabolic activity); we know it makes a great many round trips through the capillaries for about four months; then it disappears—how, where, why? It is by now abundantly clear that the normal red cell is by no means simply a chemical envelope containing hemoglobin; it has an intricate set of enzyme systems which in the course of a few months gradually become worn out and cannot be replaced.[13] Is the cell then recognized by appropriate cells as a dead object and phagocyted, does it become broken up and phagocyted, do tissue lysins destroy it, or is it captured and buried in the spleen? The answers to these relatively simple questions have eluded most investigators.

In discussing hemolytic anemia, however, we can at least talk of known mechanisms which render the red cell more vulnerable to destruction, even though the actual destructive mechanisms are only partially realized. Vulnerability may be inherent in the manner in which the red cell is produced, thus resulting in an intrinsically defective cell which has a shorter life span than the normal. Increased vulnerability may also be an acquired characteristic. Here, it is presumed, the red cell leaves the marrow in a normal state but then becomes injured in various extramedullary areas by extrinsic mechanisms. Thus in hemolytic anemia we may discriminate between those cases due (1) to intrinsic defects of the red cell and (2) to extrinsic factors which attack the normal red cell.

"INTRINSIC" HEMOLYTIC ANEMIAS

Erythrocytes appearing in the circulation as intrinsically defective units are ordinarily the end products of an inherited abnormality. To a large extent, therefore, the "intrinsic" hemolytic anemias are synonymous with the hereditary disorders. The hereditary disorder that has had the largest study and is perhaps the best known is spherocytosis (congenital hemolytic jaundice). Here, the early nucleated red cells in the marrow are of normal size and shape but there is a definite although slight reduction in the size of the late normoblast. The final non-nucleated red cell is smaller and thicker (i.e., spherocyte) than the similarity mature normocyte produced by the normal marrow. Crosby has suggested that the "hereditary" spherocyte[14] has less surface for its "contents" than does the normal cell, with the result that the membrane is stretched tightly around a bulging inner "core." In any event, there can be no doubt from a number of different studies[15,16] that the hereditary spherocyte is not only unusually fragile to hypotonic salt solutions but that its tendency to hemolysis is increased by incubation in the warm test tube and therefore presumably in the spleen. Due apparently to its relatively globular character, the spherocyte is trapped by the spleen, *any* spleen, whether in the affected individual or in a normal individual. When blood from an individual with hereditary spherocytosis is transfused into a normal individual possessing a spleen, the survival time of the transfused red cells is distinctly shorter than normal. When the same spherocytic blood is transfused into a splenectomized individual, the red cell survival time of the transfused cells is normal. Thus the spherocytes may be said to be selectively removed from the general circulation into the splenic pulp where they incubate and eventually hemolyze. In so doing, the life span of the spherocyte is naturally much shorter than that of the normal erythrocyte. Presumably, the most marked spherocytosis is accompanied by the highest degree of trapping and the greatest rapidity of destruction.

From the standpoint of hemolysis, the peculiar globular shape of the cell is undoubtedly important in hereditary spherocytosis but the shape characteristic appears to be less important in the other intrinsic disturbances. In hereditary leptocytosis or Mediterranean anemia (thalassemia), the red cell is unusually thin and, as such, unusually resistant to hypotonic salt solutions.[17] Nevertheless, the moderately severe and the severe forms of this disease show a well defined hemolytic component,[17] as indicated by the increased output of bile pigment in the stools and the slight though definite increase in

plasma hemoglobin.[5] That the red cell is hypotonically resistant is not necessarily of importance in respect to hemolysis since the *in vitro* behavior of the red cell in artificially prepared solutions of salt may be quite different from what happens *in vivo*. Thus the unusually thin red cell may be more fragile to *intravascular* trauma or may split off small segments called schistocytes, whose destruction may indeed be responsible for the increased hemolysis present.[14] The elliptocytosis commonly present may also be conducive to a slight though definite increase in hemolysis, and the presence of coarsely stippled red cells may indicate a more fundamental and inherent disturbance of hemoglobin formation, possibly with some degree of heme diversion thus leading to an increased output of bile pigment.

Mechanisms of a somewhat similar type may well be present in the other hemoglobinopathies, since in all of them (whether due to the presence of sickle (S) C, D, E or other types of hemoglobin, or their mixtures) target cells are a prominent feature. However, in sickle-cell anemia, in the sickle-cell-thalassemia disorder and in the other disorders in which sickle cell hemoglobin is a factor, there is the important additional feature of the peculiar manner in which sickled red cells aggregate and form rigidly viscous conglomerates, particularly in relatively anoxic environments.[18] Under such conditions the piling up of relatively rigid masses of red cells in small blood vessels leads not only to thrombotic manifestations but to hemolysis of injured red cells as well. Such phenomena are probably responsible for the "crises" of severe sickle-cell anemia.

In both Mediterranean anemia and sickle-cell anemia (and presumably in related states), there is a slight but definite increase in plasma hemoglobin, up to levels of 60 mg./100 cc. In one case of Mediterranean anemia studied the plasma hemoglobin definitely increased after splenectomy.[5] This suggested that abnormal red cells previously destroyed in the spleen, presumably schistocytes, were now being destroyed within the circulation.

The "intrinsic" defects of the red cell thus far discussed are inherited, ordinarily by well defined genetic mechanisms. Hereditary spherocytosis is inherited from either the mother or father of the patient, resulting in a mild, moderate or severe degree of red cell abnormality. In hereditary leptocytosis (Mediterranean anemia) and in the other hemoglobinopathies the inheritance is somewhat more complex in that the relatively mild disturbance ("trait") is inherited in a Mendelian dominant fashion from one or the other parent having the identical disturbance. It has been rather well demonstrated[19] that the presence of a single abnormal gene of two possible ones results in a relatively mild heterozygous disturbance (sickle cell trait, Mediterranean trait, and the like) and that the severe anemia is the result of a "double dose" of gene inherited from both the mother and the father. This is often a lethal condition and associated with the most severe degrees of hemolysis.

Another familial, apparently inherited, and intrinsic abnormality of the red cell is that of sensitivity to the drug primaquine.[20] This peculiar phenomenon was discovered when large numbers of American soldiers were given this new antimalarial drug. Certain individuals, invariably Negroes, developed an acute and more or less severe hemolytic anemia. Careful investigations of this phenomenon, chiefly by studies of the red cell survival time with radioactive chromate, demonstrated that certain apparently healthy Negroes had a red cell defect which could be demonstrated only by the administration of primaquine. It was further demonstrated by Weinstein et al. that the peculiarly sensitive red cells become rapidly hemolyzed when transfused into a normal volunteer recipient, but only when the drug was given. Although the exact nature of the inborn erythrocytic defect is still a mystery, it is thought to be due to a deficiency of certain enzyme systems.[20]

Although intrinsic abnormalities of the red blood cell are usually inherited, they are occasionally seen as an acquired characteristic. Thus an individual previously healthy may, as the result of completely obscure mechanisms, develop a self-perpetuating disturbance of the red blood cells, as in paroxysmal nocturnal hemoglobinuria. That the red cells of this disease are abnormal is readily demonstrated by at least two features: (1) they are more readily hemolyzed in dilute acids than are normal cells, and (2) their survival time, upon transfusion to a normal individual, is greatly diminished. This acquired characteristic, once developed, is almost always permanently retained. In pernicious anemia, on the other hand, the acquired erythrocytic defect is lost when the patient is given sufficient liver extract or B_{12}.

"EXTRINSIC" HEMOLYTIC ANEMIAS

Thus far in our discussion we have been dealing with conditions in which the red cell produced by the marrow is inherently or intrinsically defective and as such is vulnerable to premature destruction. In the other broad group of the hemolytic anemias, the red cell on its entrance into the blood from the marrow may be thought of as being normal, but at some time during its life span is attacked by some extrinsic mechanism. As the result of this attack the red cell life span is appreciably shortened and the curve of destruction is a curved one ("exponential").[4] As suggested by Ponder,[13] "acquired" hemolytic anemia may be compared to an epidemic attacking a relatively defenseless population living on a desert isle. There is a quick decimation affecting all age groups, but then the survivors, presumably the youngest and the hardiest, outlast the initial onslaught of the attack and the sharp downward slope of destruction becomes slowed.

Extrinsic mechanisms resulting in increased red cell destruction are numerous and varied. Probably the most common of these is the malarial parasite. Others include such infectious agents as the Bartonella bacillus, B. Welchii and, possibly, certain viruses. Some chemicals such as the sulfonamides can apparently act upon the red cells directly, leading to their destruction. Moth ball ingestion, as occasionally practiced by children, may result in severe hemolytic anemia.[21] Of greatest interest, however, is the immunologic mode of attack, seen clinically in the form of both *iso-* immune and *auto*-immune disorders. Iso-immune hemolytic disease is typified by erythroblastosis fetalis, in which an antibody is built up in the mother which is injurious to the red blood cells of her own infant. In the auto-immune disorders (acquired hemolytic anemia), antibodies are built up which are injurious to the individual's own red cells. The methods of auto-immunization are quite obscure but it may be postulated that certain red cells may become sufficiently altered to become antigenic. Alterations in red cell surface may conceivably occur when the cells are exposed to certain viral or other infections, or to chemicals or even malignant neoplasms or leukemias. Under such circumstances the altered red cells may not be "recognized" by the phagocytic and antibody-producing cells throughout the body,[22] with the result that a specific protein (antibody) is built up against them. Another mechanism might be through that of a hapten (virus, chemical, etc.) combining with the cell, the hapten-cell combination then becoming antigenic and producing a specific abnormal protein. Such a situation is clearly seen in the development of the quinidine-platelet antibody in individuals developing thrombocytopenic purpura upon repeated administration of quinidine.[23]

There is evidence that antibody production takes place in various white cell "systems," notably the reticulo-endothelial, the lymphocytic and the plasmocytic. In recent years increasing attention has been paid to the system of plasma cells as the chief source of antibody production. Much direct and indirect evidence has been developed demonstrating the striking correlation between hyperplasia of plasma cells, globulin production and antibody formation.[24] Electron microscope studies of plasma cells by Braunsteiner[25] have revealed a remarkable secretory structure resembling that seen in thyroid and pituitary cells. In any event, the antibodies produced by these cells have the capacity to attack not only the individual's own cells but red cells of all humans, whatever the blood group. They are, however, specific for red cells. The antibody appears to be firmly attached to receptor groups of the red blood cell and *in vitro* cannot be displaced by repeated washings with salt solution. Being a globulin, the antibody adherent to the surface of the red cells reacts with human *anti*-globulin serum (usually prepared in rabbits) with the result that agglutination takes place in the test tube (positive Coombs test).[26] Cells coated with auto-antibody are either injured directly because of this coating or only after becoming agglutinated in masses. Agglutinated red cells are probably immediately vulnerable, and thus easily lysed by such factors as complement and mechanical trauma. This can be demonstrated readily *in vitro*.[27] Cells that have been insufficiently injured to become hemolyzed may be demonstrated as *spherocytes*, and therefore a spherocyte may be thought of as a cell on its way to destruction. These partially hemolyzed red cells are presumably trapped in the spleen, thus resulting eventually in their complete destruction, or they may be phagocyted by other body cells.

In the auto-immune disturbances one may speak of two phases of hemolysis: (1) the attack phase and (2) the phase of actual lysis. The attack may be said to occur when antibody

comes in contact with red cell, with its resultant firm fixation to the cell surface. As already noted, this fixation of antibody results either in agglutination or in rendering the cell vulnerable for eventual hemolysis. The mechanisms by which actual lysis, the second phase, takes place are not clearly known, and probably vary from case to case. In the presence of a "complete" or lytic antibody, however, complement evidently completes the lysis of the sensitized, agglutinated red cells. Since most auto-antibodies are not of the lytic but of the agglutinating variety, lysis under these conditions is somewhat more difficult to explain. We have demonstrated that agglutinated red cells coated by antibody have an increased mechanical fragility, and it is very likely that the trauma of repeated passage through small capillaries leads to a certain degree of destruction.[27,28] Tissue lysins acting upon antibody-coated red cells may also be of some importance[29] and the spleen may function not only as a tissue lytic agent but as a trapping organ for already injured red cells, thus leading to lysis. True phagocytic mechanisms may also be of importance, as emphasized in a number of recent articles.[28,30,31] In any event, the auto-immune antibody mechanism, when it is fully operative, eventually leads to more or less rapid destruction of the cells within the circulation. In the presence of extremely rapid destruction, hemoglobinemia will ensue but ordinarily the degree of this abnormality is rather small since the great bulk of the increased hemolysis seems to take place through normal channels, thus leading to the production of excessive quantities of bile pigments.

Numerous types of hemolytic antibodies have been differentiated[32] but, in general, they may be divided into the following categories: (1) Agglutinating: warm and cold, (2) hemolysins. A number of different varieties may be further distinguished. For example, some agglutinating antibodies are "complete," i.e., will function against red cells in salt solution; while others are "incomplete" and can be demonstrated *in vitro* only by the use of a protein-rich medium. Some cold hemagglutinins appear to react only at very low temperatures, whereas others have a high thermal amplitude (from 3° to 37°C.) Some hemolysins, i.e., the Donath-Landsteiner hemolysin, require cold for their adhesion to the red blood cell, but warmth together with complement is essential for the eventual lysis. Other hemolysins are best demonstrated in a slightly acid medium, etc.[33] In some instances, agglutinins and hemolysins are "mixed" and it is only by careful fractionation that the differences can be detected. This is noted in certain conditions in which a high concentration of cold hemagglutinin is present. It is only by careful testing that an hemolysin, usually of the "acid" type, may be demonstrated.[34]

The auto-immune hemolytic anemias are ordinarily recognized by the simple screening maneuver of the Coombs' test. By and large, the "intrinsic" hemolytic processes are Coombs-negative, the "extrinsic" ones Coombs-positive. This rule has many exceptions. Thus, the Coombs test may be positive occasionally in the crisis of hereditary spherocytosis, indicating possibly that an immunologic difficulty has become engrafted upon an intrinsic defect. Many cases of acquired, "extrinsic" hemolysis are Coombs-negative: the hemolytic transfusion reactions, chemical poisoning, bacterial and viral infections, and hypersplenism. Hypersplenic hemolytic anemia is apparently due to the unusually marked hemolytic activity present in some splenomegalies. In these cases the red cell survival time is definitely shortened and all the various features of hemolysis are present, but the Coombs test is negative. Usually, leukopenia, granulocytopenia and thrombocytopenia are present, indicative of hypersplenic effects on the other cellular constituents of the marrow (and blood).

The hemoglobinurias are generally placed in a separate category from the more usual types of hemolytic anemia but it is likely that similar mechanisms—inherited traits, extrinsic mechanisms, including the immunologic—are operative. Intrinsic defects are probably responsible for such peculiar disorders as paroxysmal march hemoglobinemia and the primaquine hypersensitivity of the red cells occurring in certain Negroes. The nature of these defects is quite obscure, as is that of the acquired but nevertheless intrinsic erythrocytic abnormality which occurs in paroxysmal nocturnal hemoglobinemia.

Quite in contrast are the extrinsic mechanisms responsible for hemoglobinemia and hemoglobinuria. Sharp violent blood breakdown, as in hemolytic transfusion reactions or occasionally in certain cases of auto-immune hemolytic disease, may result in hemoglobinemia and hemoglobinuria. Paroxysmal cold hemoglobinuria, as classically described by Donath and Landsteiner, is due to the development of an

auto-hemolysin in the course of a syphilitic infection. How this auto-immune process is induced is quite obscure, although the complex character of the hemolysin has been thoroughly studied. In this condition one sees quite clearly the distinction between the "attack" phase of hemolysis, i.e., the auto-antibody becoming adherent to the red cell at cold temperature, and the actual phase of lysis, as induced by other mechanisms such as warmth and complement activity. Another form of paroxysmal cold hemoglobinuria is associated with the presence of a very high concentration of cold hemagglutinin. In an individual having such an antibody exposure to cold results in agglutination of large numbers of cells, particularly those at the surface of the body. This phenomenon can actually be demonstrated microscopically by slit-lamp examination of corneal blood vessels or by capillary microscopy of the nail-bed capillaries.[28] Striking, although reversible, agglutination takes place with cold. The agglutinated masses of red cells are undoubtedly readily traumatized by the circulatory pulsations taking place within the capillary loops with the result that a certain degree of hemolysis takes place. The effects of cold on a large segment of body under such conditions are readily demonstrated when one arm is placed in ice water and a tourniquet placed about it. The plasma hemoglobin rises to rather high levels (150 mg. or over) in the refrigerated arm as compared with an insignificant increase in the control arm. The effects of the antibody (cold hemagglutinin in this instance) are to become attached to the red cells, thus leading to their agglutination. The actual lysis which then takes place is the result of the activity of such other mechanisms as mechanical trauma, the effects of tissue lysins, etc.

The blackwater fever of certain cases of malaria may also be due to the development of an auto-immune mechanism, whether directly related to the disease malaria or to its conjunction with quinine administration. If an immunologic mechanism is present, its nature is obscure, although it seems unlikely that the hemoglobinemia is due to the effects of the malarial parasite alone. The fact that quinine is a possible factor in many cases suggests the possibility of a phenomenon somewhat similar to that recently studied in primaquine erythrocytic sensitivity. It also brings to mind the known effects of both quinine and its isomer quinidine in bringing about thrombocytopenic purpura in individuals who have had several administrations of the drug. In the latter cases, it has been amply demonstrated that an abnormal auto-antibody is built up which acts only in the presence of quinine or quinidine and causes (with complement) eventual lysis of large numbers of platelets and thus thrombocytopenia.

MULTIPLE AUTO-IMMUNE MECHANISMS

As knowledge of pathogenetic mechanisms in hemolytic anemia has advanced, particularly in the acquired forms, it has become apparent that auto-immune mechanisms are also operative in certain cases in which the hemolytic disturbance is only one feature of the disease. Thus Evans[35] pointed to the occurrence of cases showing both an auto-immune hemolytic anemia with positive Coombs test and thrombocytopenia purpura. He postulated that the thrombocytopenia might also be due to the presence of platelet antibodies and that idiopathic thrombocytopenic purpura (ITP) might well be "immunothrombocytopenia." His deductions have been in large measure responsible for the present concept of ITP as an immunologic disease due to the development of platelet auto-antibodies causing platelet destruction. These concepts have been abundantly confirmed by Harrington et al.[36] and in our own laboratory.[37] We have observed the "double" mechanism of auto-immune disease (Evans' syndrome) in six cases in the past few years, a not inconsiderable number during a period when forty cases of simple auto-immune hemolytic anemia were found. A probably triple auto-immune disorder involving three tissues, i.e., red cells, platelets and small blood vessels, is that of thrombohemolytic thrombocytopenic purpura. Here there is a more or less simultaneous involvement of three separate tissue groups, either by a single immunologic abnormality or by multiple ones. As yet, all studies attempting to demonstrate the presence of auto-antibodies have been fruitless, but short red cell and platelet survival times, indicating an extrinsic mechanism acting upon these cells, have been demonstrated.[38] The blood vessel lesions of this disease resemble to some extent those of periarteritis nodosa, and in the latter disease hemolytic anemia occurs not infrequently (observed four times in our series). In disseminated lupus, another of the so-called collagen disorders, a positive Coombs test is quite common and auto-immune hemolytic

anemia is not infrequently seen. In fact, many immunologic disturbances can be demonstrated in this disease: the positive L.E. phenomenon, leukopenia, auto-immune hemolytic anemia, apparently typical ITP, auto-immune (anticoagulant) hemolytic disease, etc.[39] So much is this true that if one observes a case of apparently typical auto-immune hemolytic anemia, and especially one with multiple sensitizations (positive serologic reactions, positive heterophile reaction, etc.), the distinct possibility that one of the generalized collagen diseases, such as disseminated lupus, is present should be seriously considered. At times this cannot be demonstrated, even by several L.E. tests, but will only come to light with splenectomy, when the typical lesions of disseminated lupus in the spleen are noted. In three of our cases, showing only hematologic features before splenectomy, the characteristic disseminated lesions of lupus developed after the operation, indicating a possible "inhibitory" effect of the spleen on the lupus process. This is reminiscent of the Bartonellosis developing in rats after splenectomy; for this phenomenon a humoral factor in the spleen has been demonstrated by experiments with parabiosis.[40] How lupus brings about auto-immune hemolytic anemia is obscure, but it is probable that the lupus patient is a very strong antibody producer, with the result that auto-immune mechanisms are produced affecting many of the patient's tissues.

Some cases of apparently typical auto-immune hemolytic disease are associated with chronic lymphocytic leukemia and lymphosarcoma.[41] The mechanism by which an auto-antibody attacking the red cells is produced in these cases is also quite obscure, but it may bear some relationship to the possible production of abnormal protein factors by a widely proliferating group of lymphocytic cells.

From these fragmentary observations, and many others, it has become clear that the auto-immune mechanism is an important one in the production of various kinds of human diseases. Such mechanisms have been rather readily demonstrated in hemolytic anemia, less so in thrombocytopenic purpura and in certain instances of leukopenia and vascular purpura. It is possible that they are at the basis of many types of renal disease, rheumatic fever and rheumatoid arthritis, ulcerative colitis, periarteritis nodosa, disseminated lupus and other collagen disorders. The auto-immune concept of disease, in which an auto-antibody somehow develops, following an initial insult of some other process (chemical, viral, bacterial, etc.) bears watching for important future developments.

SUMMARY

Hemolysis, which is a normal physiologic process, increases under certain abnormal conditions when the red cell, for one reason or another, is vulnerable and has a shortened life span. Increased hemolysis results in such direct indications of red cell breakdown as hemoglobinemia, increased fecal urobilinogen output and spherocytosis, and in many indirect phenomena, including chiefly reticulocytosis. The red cell is either *born* vulnerable (intrinsic defects, hereditary genetic mechanisms) or *becomes* so under the influence of various extrinsic factors. Of the latter, the immunologic ones, particularly of the auto-immune variety, are of greatest interest. There can be no question now that *auto*-immune mechanisms develop in the course of several diseases, resulting in an attack on such tissues as the red cells, the leukocytes, the platelets, etc. How the auto-immune antibody develops is a matter of conjecture but presumably it originates when the specific cell concerned is sufficiently altered to become antigenic. In the case of auto-immune hemolytic anemia the antibody concerned becomes adherent to the red cell, rendering it vulnerable to eventual hemolysis. This second or actual phase of hemolysis probably takes place through a number of different mechanisms including complement activity, splenic trapping of spherocytes, possible tissue lysins, and even by erythrophagocytosis. The auto-immune mechanisms may be either single or multiple, and may be responsible for many different diseases, including among others thrombohemolytic thrombocytopenic purpura, disseminated lupus, etc. Studies in hemolytic anemia have led to many important discoveries, not only in the blood groups but in the possible phenomena underlying the relatively obscure collagen disorders.

Having discussed some of the features of hemolytic disease, it may be of some value also to add a series of classifications which have been found useful, particularly in teaching and in obtaining a "bird's-eye" view of a rather complex field:

I. TYPES OF HEMOLYSIS

I. "Normal" (Cellular, Reticulo-endothelial) Hemolysis	-vs.-	*II. "Intravascular" Hemolysis*
Normally		Hemoglobinemia
Most cases of hemolytic anemia		Hemoglobinuria

II. "CLASSICAL" CLASSIFICATION

I. Hereditary	*II. Acquired*	*III. Hemoglobinurias*
Spherocytosis	Chemical	Paroxysmal march
Leptocytosis (Mediterranean anemia)	Bacterial, viral	Paroxysmal cold
Sickle-cell anemia	Parasitic	with hemolysin
Other hemoglobinopathies	Immunologic:	with agglutinin
Others	Iso-immune	Paroxysmal nocturnal
	Auto-immune	Others
	Hypersplenic	

III. "MODERN" CLASSIFICATION

I. Due to "Intrinsic" Defects of the Red Cell
(Short red cell life span of patient's cells in normal circulation)
Hereditary spherocytosis
Hereditary leptocytosis (Mediterranean anemia—thalassemia)
Hereditary sickle-cell anemia
Other hereditary hemoglobinopathies (C, D, E, and combinations with thalassemia or sickle-cell disease)
Other hereditary "abnormalities":
Familial non-spherocytosis
Hereditary hypochromic anemia with high serum Fe
Others, not well classified, including primaquine hypersensitivity
Paroxysmal nocturnal hemoglobinuria

Pernicious anemia

Paroxysmal march hemoglobinuria

II. Due to "Extrinsic" Mechanisms
(Red cell life span altered by an outside factor)
Bacterial, viral
(Bartonella, B. Welchii, etc.)
Parasites (malaria)
Chemical
Auto-immune:
with agglutinins \ hemolytic anemias
with hemolysins / hemoglobinurias

Iso-immune:
Transfusion reactions
Rh disease
Others

Hypersplenic

"Symptomatic":
Disseminated lupus
Periarteritis nodosa
Lymphocytic leukemia
Lymphosarcoma
Others

IV. AUTO-IMMUNE HEMOLYTIC ANEMIA—SINGLE AND MULTIPLE TYPES

A. *Acquired Auto-Immune Hemolytic Anemia*
Acute, subacute, chronic forms
"Idiopathic" and symptomatic" (chronic lymphocytic leukemia, lymphosarcoma, carcinoma, dermoid cyst, etc.)
B. Acquired auto-immune hemolytic anemia and thrombocytopenia (Evans' syndrome)
C. Thrombohemolytic thrombocytopenic purpura
Hemolytic, thrombocytopenic and small blood vessel disturbances
D. Disseminated lupus erythematosus
Multiple auto-immune processes present, including hemolytic anemia (white cells, red cells, platelets, blood vessels, coagulant factors—all may be affected)

REFERENCES

1. Crosby, W. H. The hemolytic states. *Bull. New York Acad. Med.*, 30: 27, 1954.
2. Weinstein, I. M., LeRoy, G. V. and Necheles, T. F. Radioactive sodium chromate for the study of the survival of red blood cells. *J. Lab. & Clin. Med.*, 42: 358, 1953.
3. Ashby, W. The determination of the life of the transfused blood corpuscles in man. *J. Exper. Med.*, 29: 267, 1919.
4. Mollison, P. L. Blood Transfusion in Clinical Medicine. Oxford, 1951. Blacknell Scientific Publications.
5. Crosby, W. H. and Dameshek, W. The significance of hemoglobinemia and associated hemosiderinuria, with particular reference to various types of hemolytic anemia. *J. Lab. & Clin. Med.*, 38: 829, 1951.
6. London, I. Metabolism of hemoglobin and of bile pigment. *Bull. New York Acad. Med.*, 30: 509, 1954.
7. Singer, K., Miller, E. B. and Dameshek, W. Hematologic changes following splenectomy in man, with particular reference to the target cell, hemolytic index and lysolecithin. *Am. J. M. Sc.*, 202: 171, 1941.
8. Hagen, P. S. and MacDonald, R. M. Fecal urobilinogen excretion in hemolytic anemia: comparison with results of average red cell life span

determined by radiochromium red cell tagging. *J. Lab. & Clin. Med.*, 44: 807, 1954.

9. Tat, R. J., Greenwalt, T. J. and Dameshek, W. Output of bile pigment by newborn infants and by older infants and children. *Am. J. Dis. Child.*, 65: 558, 1943.
10. Dameshek, W., Greenwalt, T. J. and Tat, R. J. Erythroblastosis fetalis (acute hemolytic anemia of the newborn). *Am. J. Dis. Child.*, 65: 571, 1943.
11. Dameshek, W. and Schwartz, S. O. Acute hemolytic anemia (acquired hemolytic icterus, acute type). *Medicine*, 19: 231, 1940.
12. Suess, J., Limentani, D., Dameshek, W. and Dolloff, M. J. A quantitative method for the determination and charting of the erythrocytic hypotenic fragility. *Blood*, 3: 1290, 1948.
13. Ponder, E. Certain hemolytic mechanisms in hemolytic anemia. *Blood*, 6: 559, 1951.
14. Crosby, W. H. The pathogenesis of spherocytes and leptocytes (target cells). *Blood*, 7: 261, 1952.
15. Young, L. E., Izzo, M. J. and Platzer, R. F. Hereditary spherocytosis. *Blood*, 6: 1073, 1099, 1951.
16. Emerson, C. P., Jr., Shen, S. C., Ham, T. H. and Castle, W. B. The mechanism of blood destruction in congenital hemolytic jaundice. *J. Clin. Investigation*, 26: 1180, 1947.
17. Dameshek, W. Familial Mediterranean target-oval cell syndromes. *A. J. M. Sc.*, 205: 643, 1943.
18. (*a*) Murphy, R. C. and Shapiro, S. Pathology of sickle cell disease. *Ann. Int. Med.*, 23: 376, 1945; (*b*) Singer, K. The pathogenesis of sickle cell anemia. *Am. J. Clin. Path.*, 21: 858, 1951.
19. (*a*) Neel, J. V. Perspectives in the genetics of sickle cell disease. *Blood*, 7: 467, 1952; (*b*) Neel, J. V. and Valentine, W. N. Further studies on the genetics of thalassemia. *Genetics*, 32: 38, 1947.
20. (*a*) Dern, R. J., Weinstein, I. M., LeRoy, G. B. Talmage, D. W. and Alving, A. S. The hemolytic effect of primaquine. I. The localization of the drug-induced hemolytic defect on primaquine-sensitive individuals. *J. Lab. & Clin. Med.*, 43: 303, 1954; (*b*) Dern, R. J., Beutler, E., Flanagan, C. L. and Alving, A. S. Studies of the acute hemolytic anemia induced by certain aniline derivatives and related compounds. *J. Lab. & Clin. Med.*, 44: 788, 1954; (*c*) Beutler, E., Dern, R. J., Alving, A. S. The hemolytic effect of primaquine. IV. The relationship of cell age to hemolysis. *J. Lab. & Clin. Med.*, 44: 439, 1954.
21. Zuelzer, W. W. and Apt, L. Acute hemolytic anemia due to naphthalene poisoning. *J. A. M. A.*, 141: 185, 1949.
22. Burnet, F. M. and Fenner, F. The Production of Antibodies. Melbourne & London, 1953. Macmillan & Co.
23. Dameshek, W. Hemotoxic reactions to drugs. *Postgraduate Med.*, 16: 369, 1954.
24. Barr, D. P. The function of the plasma cell. *Am. J. Med.*, 9: 277, 1950.
25. Braunsteiner, H., Fellinger, K. and Pakesch, F. Demonstration of a cytoplasmic structure in plasma cells. *Blood*, 8: 916, 1953.
26. Coombs, R. R. A., Mourant, A. E. and Race, R. R. A new test for the detection of weak and incomplete Rh agglutinins. *Brit. J. Exper. Path.*, 26: 255, 1945.
27. Dameshek, W. and Miller, E. B. Pathogenetic mechanisms in hemolytic anemias. *Arch. Int. Med.*, 72: 1, 1943.
28. Wasastjerna, C. Immunohemolytic mechanisms *in vivo*. The mode of destruction of sensitized red cells in the living organism. *Blood*, 8: 1043, 1953.
29. Castle, W. B., Ham, T. H. and Shen, S. C. Observations on the mechanism of hemolytic transfusion reactions occurring without demonstrable hemolysin. *Tr. A. Am. Physicians*, 63: 161, 1950.
30. Zinkham, W. H. and Diamond, L. K. *In vitro* erythrophagocytosis in acquired hemolytic anemia. *Blood*, 7: 592, 1952.
31. Bonnin, J. A. and Schwartz, L. I. The combined study of agglutination, hemolysis, and erythrophagocytosis, with special reference to acquired hemolytic anemia. *Blood*, 9: 773, 1954.
32. (*a*) Dacie, J. V. and DeGruchy, G. C. Auto-antibodies in acquired hemolytic anemia. *J. Clin. Path.*, 4: 253, 1951; (*b*) Dacie, J. V. Acquired hemolytic anemia, with special reference to the antiglobulin (Coombs') reaction. *Blood*, 8: 813, 1953; (*c*) Dameshek, W. Acquired hemolytic anemia—physiopathology with particular reference to autoimmunization and therapy. Proceedings of the Third (1950) International Congress of the International Society of Hematology, Cambridge, England. New York, 1951. Grune & Stratton.
33. Gardner, F. H. and Harris, J. W. The demonstration of hemolysis in acquired hemolytic anemia. *J. Clin. Investigation*, 29: 814, 1950.
34. Dacie, J. V. The presence of cold hemolysins in sera containing cold haemagglutinins. *J. Path. & Bact.*, 62: 241, 1950.
35. Evans, R. S., Takahashi, K., Duane, R. T., Layne, R. and Liu, C. K. Primary thrombocytopenic purpura and acquired hemolytic anemia—evidence for a common etiology. *Arch. Int. Med.*, 87: 48, 1951.
36. Harrington, W. J., Minnich, V., Hollingsworth, J. W. and Moore, C. V. Demonstration of a thrombocytopenic factor in the blood of patients with idiopathic thrombocytopenic purpura. *J. Lab. & Clin. Med.*, 38: 1, 1951.
37. Stefanini, M., Dameshek, W., Chatterjea, J. B., Adelson, E. and Mednicoff, I. B. Observation on the properties and mechanism of action of a potent platelet agglutinin detected in the patient with idiopathic thrombocytopenic purpura (with a note on the pathogenesis of the disease). *Blood*, 8: 26, 1953.
38. Adelson, E., Heitzman, E. P. and Fennessey, J. F. Thrombohemolytic thrombocytopenic purpura. *Arch. Int. Med.*, 94: 42, 1954.
39. Dameshek, W. (*a*) Immunohematology. *J. Indian M. Profession*, 1: 263, 1954; (*b*) Immunohematologia. In Interlingua: Proceedings of the Fifth Congress of International Society of Hematology at Paris, 1954.
40. Lauda, E. Die normale und pathologische Physiologie der Milz. Berlin und Wien, 1933. Urban und Schwartzenberg.
41. Rosenthal, M. C., Pisciotta, A. V., Komninos, Z. D., Goldenberg, H. and Dameshek, W. The auto-immune hemolytic anemia of malignant lymphocytic disease. *Blood*. In press.

Conference on Therapy

Surgical Treatment of Mitral Valvular Disease

THESE are stenographic reports, which have been edited, of conferences by the members of the Department of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. GEORGE READER: We are particularly fortunate in having Dr. Frank Glenn to open the discussion on mitral valvulotomy in mitral stenosis.

DR. FRANK GLENN: Cardiac surgery has made great strides in the past several years, and particularly in the field of mitral disease. However, I think it is well for us to bear in mind that there are still many unsolved parts to this problem. It is estimated that there are over a million people in the United States with mitral stenosis, and there are probably 10,000 individuals who die each year as a result of the disease. We have no accurate information about the total disability or man days of work that are lost, but all are agreed that prevention would be the best treatment. Until such time as we are able to do this we are confronted with taking care of the scarred and stenosed mitral valve of the patient who has had rheumatic fever.

In this institution we have pursued a fairly systematic approach to the management of these patients. Most of them are referred to us either from outside the institution or from our own clinic. Each patient that we undertake to consider is carefully evaluated as to history, physical findings, with particular respect to the heart, the state of compensation, electrocardiogram, x-ray of the chest and fluoroscopy, angiocardiogram in certain cases and, finally, when indicated, the results of cardiac catheterization. This last is perhaps the most crucial bit of information that we are able to obtain among these patients who are having difficulty in deciding whether or not they should be operated upon. By this method we can determine the cardiac output, pulmonary artery pressure, detect evidence of mitral insufficiency and tricuspid disease and, something that is of great importance, the response of cardiac output and pulmonary artery pressure to exercise. We have been fortunate in having as head of our cardiophysiologic unit Dr. Daniel Lukas who, as you know, has contributed much to this field.

The ideal patient for surgery is one with pure mitral stenosis exhibiting symptoms and manifestations that one would expect should be improved by enlargement of the mitral orifice. Up to the present time we have not operated upon any patients who have mitral stenosis but are without symptoms. It is not easy to set up absolute criteria at this stage and the clinical impression still plays a major role in making our decision. We have included patients with a predominant lesion of mitral stenosis but with minimal mitral insufficiency. The degree of regurgitation, as judged by the regurgitant stream at operation, has not always agreed with either the estimate made from the murmur and enlargement of the left ventricle, or with the estimate made from the catheterization pressure curves.

From this group of patients who exhibit predominant mitral stenosis, we have accepted for operation those with auricular fibrillation as well as those with normal rhythm; patients whose hearts were large as demonstrated by x-ray, fluoroscopy, electrocardiogram and physical examination, provided enlargement did not point to predominating mitral insufficiency or to advanced aortic lesions. We have accepted patients with minimal aortic lesions, namely, insufficiency with or without stenosis, if the predominant lesion was mitral stenosis, and

those with a history of hemoptysis indicating an increase in pulmonary artery pressure which might be reduced by enlarging the mitral orifice. We also accept patients with a history of pulmonary edema, pulmonary infarction or subacute bacterial endocarditis. Patients with functional tricuspid insufficiency were not ruled out on the basis of this lesion alone, however. Age alone was not a determining factor in the patients we have selected, but the opinion of the anesthetist as to whether or not the patient could tolerate anesthesia was an important factor in our decisions. Patients have been accorded the usual medical therapy until considered to be in the best possible condition for the operation. Finally, prior to operation a conference is held on most patients by our interdepartmental cardiovascular group made up of representatives of medicine, pediatrics, surgery and the cardiophysiologic group, in conjunction with the anesthetist and the surgeons.

As far as the operation is conerned, the surgery of mitral disease is dependent upon the anesthesia. In this group of patients, particularly with a very low cardiac reserve, a malfunctioning heart is a common finding, as is a poorly functioning pulmonary system as the result of hypertension and sclerosis. A thorough understanding of these physiologic changes on the part of the anesthetist is essential, and expert administration of the anesthetic agent to maintain a high oxygen concentration in the blood is of the greatest importance. Our patients have had the benefit of meticulous induction and maintenance of a light anesthesia by our Chief of Anesthesiology, Dr. Joseph F. Artusio.

When preparing the patient for operation, provision is made for rapid and adequate blood replacement by suitable methods. Several liters of blood are kept at hand during the operation, to be given rapidly under pressure should the washing out of intra-auricular thrombi or inadvertent injury cause a loss of blood. Any blood loss is carefully estimated as the operation proceeds by weighing all sponges and by measuring any blood removed by suction.

After induction of anesthesia, with the patient in position, the left thorax is slightly elevated on a folded sheet placed under it from the shoulder to the level of the twelfth rib. The heart is approached through a left anterior, lateral incision. The heart is inspected; and then while the anesthetist exerts pressure upon the carotid vessels, we palpate the left auricular appendage to determine whether there are clots present, exercising care not to dislodge clots if they happen to be present. Thereafter we place two purse-string sutures around the base of it and a clamp just at the distal portion, and then we excise the tip of it. If we think there are clots in the auricular appendage, we insert our finger carefully as we try to break up these clots and allow them to be washed out, losing probably 50 to 75 cc. by each manipulation. Once inside the auricle, we are interested in evaluating the stenosed valve. No two valves are alike. The first thing we are interested in, is there or is there not regurgitation. If there is much regurgitation, our hearts sink a little; we know that our prognosis is not as good as when we have a pure mitral stenosis. A small amount is perfectly all right. You then palpate the valve. You determine first the size of the orifice then the mobility of the two component leaves, and then you look for calcific deposits. Having gotten that information, you proceed to enlarge this orifice which, in the majority of our patients, is less than 1.5 square cm. in area. This is accomplished by simply introducing the finger into the orifice and fracturing the valve. Occasionally the valve's diameter cannot be increased by finger fracture alone, so a valvulotome of the Bailey or Harken type is used to increase the area of the orifice at the line of the presumed commissure. It is our objective to increase this orifice from, we will say, 1.5 square cm. area to 4 to 6. Generally speaking, in the pure mitral stenosis we do not end up with any insufficiency. If a slight degree of insufficiency is present, it may be corrected by overcoming the stenosis; if there is very much insufficiency, the chances of decreasing it are scant indeed. We have operated upon patients we knew had some mitral insufficiency. We have not always estimated correctly. In some of these patients we found more stenosis than we had anticipated; in others we found more insufficiency than we anticipated. Following the necessary enlargement of the orifice, the finger is withdrawn and the auricular appendage is occluded by tightening up the purse-string sutures at the base of the appendage and oversewing the tip. If we occlude, by pressure or distortion, the coronary vessels near the base of the appendage, cardiac arrest may occur. We had two such patients whom we were able to resuscitate successfully without residual damage. This is, then, one of the places where the patient may get into difficulty. I cannot

overemphasize the importance of the anesthesia in the operative procedure. In the very successful method used by Dr. Artusio he is able to talk to his patients throughout the procedure, although they do not remember their experience.

As far as postoperative complications are concerned, I would say that the immediate course of these patients is usually predictable according to what you find at operation and your previous evaluation. Regular hearts become irregular after this procedure, but many of these return to normal rhythm. We are always concerned about the possibility of pulmonary edema and we watch our patients very closely not to overload the circulation. We place them in an oxygen tent merely to take as much load off the heart as possible. Pain is always a factor immediately after operation and in 15 to 20 per cent of patients for weeks afterward, so that it has come to be known as the postoperative cardiac pain syndrome. This is most marked in the substernal area and over the anterior left chest. Nerve block has been used but is not always efficacious. We are unable to explain the mechanism of this syndrome.

As to results, we have operated upon over 130 patients. Up to the present time we have lost three patients. The first of those was lost without evident explanation. The patient was a relatively young man, age thirty, one of the first ten we did. No autopsy was obtained. The second patient to die was a woman who was in her late forties, whom we had rejected eight months before. She had had multiple emboli. She went through the operation well, had returned to the medical floor with some improvement and had been mobilized. She died, I think it was, on her twenty-first postoperative day. Autopsy revealed an intracranial hemorrhage. We lost a patient on the table, an individual with regurgitation, advanced myocardial damage and a great deal of calcification in the valve. She sustained a cardiac arrest on the operating table and we were not able to resuscitate her. This low mortality rate I am sure would, if publicized, lead to the impression that our patients have been of a good risk group. I can assure you that we have not withheld surgery from any patient when we believed there was a reasonable opportunity to provide some help. The credit for the low mortality goes to all of those that have been concerned in the care of these patients. The first 100 patients all had cardiac catheterization. Since then we have been selecting the patients that we think it absolutely necessary to subject to this ordeal. The use of the angiocardiogram enables us to visualize the left auricle better and gives us some information as to the size of the valve.

I am very greatly encouraged by the results, much more than I was eighteen months ago. We used to think that the improvement would be immediate. As a whole, the patients have continued to improve for a period of two years after operation, and many patients who have not had marked improvement for the first three months have improved thereafter. Dr. Stewart and his group are evaluating our patients at the present time. I think we probably will be able to show that we have definitely benefited about 70 per cent of the patients, or better. We have operated upon patients whom, in the future, I think we will not operate upon.

I think the ideal patient for operation is one who has a valve that you can really do something with. It is found in the relatively young person and in the person who has had marked decrease in functional capacity over a period of not more than about eighteen months or two years. Operating upon the older patient—when I say older I am not referring to a specific age but to those individuals in whom a disease process has been going on for a long time—will never be as satisfactory as operation on the lesion which has been more recently established. The possibilities of the future in this I think are going to be increased by open cardiac surgery. Mitral insufficiency, which has been thus far ineffectually met surgically, I forecast will be successfully dealt with in the next few years.

It is well for us to bear in mind, in considering patients for surgery, that patients do die quite unexpectedly because of their mitral stenosis. I will tell you of a patient we had about a year ago, a young Negro girl. I believe her age was about twenty-seven. She was brought into the hospital for study and was carefully evaluated. Her mitral valve was calculated by Dr. Lukas as being 0.9 square cm. in area. She was considered in our conference on Wednesday. There was some discussion as to whether or not she had been given an adequate amount of digitalis. We therefore decided to postpone our operation until the following week. At that time she had bathroom privileges but spent most of her time in bed. On the following Sunday morning she became nauseated and we

thought she received too much digitalis. She was told to stay in bed. To make a long story short, she went into pulmonary edema and died within eight hours. At postmortem examination the measurement of the valve orifice was exactly what Dr. Lukas had forecast. I am convinced that if we had operated upon that patient before this episode, she would have survived and would have had a good result because she had a valve that could be split, one without calcification, and a good myocardium.

DR. READER: Thank you, Dr. Glenn. That is a most remarkable record. Are there questions?

VISITOR: What do you assume to be the reason for failure of improvement in the remaining 30 per cent of the cases? Do you assume that the operation failed to enlarge the valve?

DR. GLENN: About 50 per cent of patients are improved enough to have the Heart Association classification changed one category; another 20 per cent are improved but not that much. Perhaps it would be well for me to say a word about that 30 per cent of failures. Many of these patients did improve but they were still disabled. The follow-up has not been long enough. I do not know how the matter will stand when a more critical evaluation is carried out in about two years after the operation. It may show that patients with insufficiency also have benefited. As to the failures in the patients with stenosis, there were some in whom we had not opened the valve sufficiently. That group might be considered for reoperation. There are those individuals with associated lesions that were more severe than we were inclined to believe prior to the operation. I do not think much can be done about that group. Also, there are those patients who have been disabled for a very long time and in whom too much irreversible damage of the myocardium has taken place. All of these together add up to about 30 per cent of the patients we have operated upon but who have not really been helped.

VISITOR: What are the subjective and objective criteria for improvement?

DR. GLENN: The most important criterion is the patient's increased capacity for work. This has to be carefully evaluated, for patients are anxious to cooperate and what they say about increased activity may prove misleading. However, the improvement is frequently so spectacular and early that there is no mistaking it. As we have watched these patients in the cardiac clinic over a period of time, now over three years, many of them have continued to improve. Once the improvement begins, it seems to continue. We have had very few patients in whom regression occurred after a brief period of improvement. Aside from this gross evidence of improvement in terms of the patient's capacity for activity, there are the various cardiac measurements which provide supportive information, proof of increased size of the valve orifice and diminished pulmonary hypertension.

DR. READER: Dr. Glenn, your remark about the information we obtain from patients sometimes proving misleading in evaluation of the effects of the operation was brought forcibly to our attention by one of your patients whom we had the privilege of following up for a period before and after the mitral surgery. It struck us that there is a psychologic factor in this matter of performance. This was a young woman who had been handicapped in all her activities until the age of thirty-five or forty. After her valvular lesion was corrected she was faced with a new difficulty, that of realizing that she could now do more than she could previously. She now could climb stairs and do other things she enjoyed doing, like dancing. By these criteria she would be considered to have shown a marked improvement as a result of the operation. It looked otherwise, however, in terms of her housework. She still could not bring herself to do housework. Her husband had always done it because she had a bad heart.

DR. GOLD: In line with Dr. Reader's example, I have one of a young man who coddled himself pretty much with his mitral stenosis. For about two years prior to the operation he no longer worked because of alleged cardiac symptoms. A successful mitral valvulotomy was performed. The objective measurements all showed improvement. He was virtually symptom-free during the first six months, when he was advised to resume his work. Now his troubles began. He developed an assortment of cardiac and vascular symptoms with anxieties and panics, a conversion neurosis, which left very little doubt that the psychologic problem of resuming work was more important than any deficiency of the heart or circulation. Without special attention to such matters as these, the operation could in a sense have been considered a failure in this patient, whereas in another sense it was really a success.

DR. GLENN: I think there is still another way of viewing these problems which may help to

avoid erroneous evaluations of the results of operation. There are many patients who are advised, and properly so, to avoid exceeding their capacity and to quit whenever they get tired. With this feeling of caution patients maintain their activities below their full capacity, and under these circumstances underestimate their capacity. In the build-up for the operation they come to believe that the result will be a greater capacity for activity and work. They try themselves out after the operation and find that they can do much more than they did before, but the capacity to do this may have been there all the time, long before the operation.

DR. GOLD: It seems to me that this discussion points up a very important aspect of the problem of evaluating the benefit of surgery in mitral stenosis, namely, an assessment of the kind of preoperative medical care and advice. One of the most significant developments in the management of heart disease in the past twenty-five years or so has been the change in attitude toward the physical capacity of patients with heart disease. It used to be popular to consider them cripples, but it is now recognized that a very high proportion possess the capacity of normal people for carrying on their life's work. Now we shall have to take care to find out whether a particular patient has really been functioning at his full capacity or much below it prior to the operation before we conclude that the operation has succeeded in enhancing his capacity. We must make every effort to ascertain how much of the apparent disability before operation had its roots in a psychic disability.

DR. GLENN: I am impressed with the importance of seeking out some criteria for operation before patients have been subjected to a prolonged period of invalidism. We had one patient in the past year who illustrates the point very well. He was a young man working in an office downtown. He was known to have had mitral stenosis for some time and was doing well with it. He then began to get into trouble and became incapacitated in a period of about six months. He began to throw off emboli. He was brought into the hospital and studied. Following cardiocatheterization more emboli developed, although I doubt this was the cause. He remained in the hospital about four months and was then sent home for a period. We have operated upon him since. He seems to be fully restored and has returned to his regular work. I do not know how long he could have tolerated the high degree of disability that he had and still be restored to reasonable activity. I believe that chronic invalidism is a great deterrent to rehabilitation. We should reduce disability prior to operation to as short a period as possible.

VISITOR: I wonder if by operating earlier in the course of the disease we might prevent the development of mitral insufficiency, which cannot be helped by the operation, or would that make no difference?

DR. WARD D. O'SULLIVAN: I do not know. I have often wondered about operating upon people at an early age. Mitral insufficiency is less apt to be present and the immediate operative result is apt to be better. The operation is more easily performed and a better job is done on young persons. Yet it may turn out that in spite of the operation the disease will follow its natural course. I certainly agree with the position that the operation should be performed on any person with mitral stenosis who has developed disability at an early age, and who is at the stage where he finds it necessary to curtail his activities or is advised to do so by the doctor.

DR. GOLD: I take it that you would prefer to postpone operation until there is clear evidence that the patient is disabled.

DR. O'SULLIVAN: Yes, not just a person who has a murmur.

DR. READER: Would you think marked reduction in the size of the mitral orifice sufficient to justify the operation even if the patient is not physically disabled?

DR. GLENN: Actually, at the present time we estimate the orifice only in those patients of whom we are uncertain, and are trying to make up our minds about. These are usually poor-risk patients. The clinical picture of incapacitation is very closely related to the size of the mitral orifice. In reference to your question, it should also be pointed out that there is more involved than just the valve leaf. I do not know this to be a fact but I should think that there is a likelihood that some patients who are operated upon young in life and with very good results may have recurring episodes of rheumatic fever. This may lead to further deterioration of the valve and more trouble.

DR. ROY C. SWAN: Dr. Glenn referred to a few patients who showed some improvement for a few months following the operation but which seemed not to last. What appears to be the reason for that kind of result?

DR. GLENN: Unfortunately, only a small number of our patients have had cardiocatheterization after the operation. There were two with this temporary improvement. We were chagrined to discover how small the valve orifice turned out to be. I have an idea that the apparent improvement in these two patients was due to a combination of psychologic factors and the benefits of rest and hospitalization. These patients are nursed and buoyed up for a period of ten days to two weeks before operation. They receive optimum care and abundant attention is paid to all their needs. Then comes the operation, hospitalization for two or three weeks, after which they are sent to a convalescent house for such a period as they elect to stay. Naturally such an individual is going to be able to put up a better front for a period of time. We have to take these factors into consideration in judging the value of enlargement of the mitral valve *per se*.

DR. READER: I take it that what you are saying is that such a period of rest and care without the operation might have resulted in similar improvement for a while. It might be well to try this in some cases.

DR. GOLD: I would like to ask Dr. Glenn whether the various measurements, including the results of catheterization, made prior to operation ever supply you with material which decides the question of operation.

DR. GLENN: Would you like to answer that, Dr. O'Sullivan?

DR. O'SULLIVAN: We performed cardiac-catheterization in every one of the first 100 cases. Some of these presented only a short history of symptoms. Fairly marked elevation of pulmonary arterial pressure was found by catheterization. We thought it proper to prognosticate that the pressure was going to continue to increase and that these would become very sick persons in the future. Here were, then, ideal candidates for the operation, namely, early symptomatology but with the suitable mechanical set-up for progression and permanent disability.

DR. GOLD: May I then ask you this: Could you not have obtained in another way information that has similar significance? Would you not learn the same things about these patients if on fluoroscopic examination you found marked straightening of the left border of the heart, an enlarged left auricle, distention of the pulmonary vessels? These are quite characteristic of mitral stenosis and develop in association with increased pulmonary pressure. Were these findings absent in your cases so that you had to depend upon the results of catheterization?

DR. O'SULLIVAN: The results of catheterization are much more decisive, much more exact. We have had some people in whom the pulmonary hypertension was very high and the mitral valve very small, but in whom the left auricle was only moderately enlarged. Perhaps the largest left auricles that we have seen have been associated primarily with insufficiency rather than stenosis. There is no relationship that I know of in the stenotic group between the size of the auricle and the degree of pulmonary hypertension.

DR. DANIEL S. LUKAS: Could I comment further on this somewhat confusing matter? We have been trying to correlate the size of the mitral valve with the pulmonary vascular pressure, the size of the left auricle and pulmonary vessels. It seemed at first that there was a fairly good correlation between the size of the mitral orifice and the size of the left auricle. This impression was not sustained as our series enlarged. The left auricle can be, surprisingly enough, quite large when the orifice of the mitral valve is only moderately reduced and, conversely, the left auricle may be only moderately enlarged in cases in which the mitral orifice is extremely small. Also, there appears to be no close relationship between the total cross sectional area of the main stem of the pulmonary artery and the pulmonary arterial pressure. In this connection it should be mentioned that the left atrium may push the pulmonary artery outward, giving the appearance of enlargement when actual measurements show that the pulmonary artery is not much enlarged. For these reasons I think we cannot evaluate the status of the mitral stenosis from the fluoroscopic examination or x-ray pictures.

In connection with the practice of catheterization, I might add that we have gotten around to doing only the problem cases now. The kind of cases that have been cropping up of late have been those in which the symptoms have been few, and in which we find striking elevation of the pulmonary arterial pressure as well as marked reduction in the size of the mitral orifice, the typical signs of the disturbed hemodynamics of mitral stenosis. In these cases the cardiocatheterization data are used to the best advantage to decide the question of operation.

DR. READER: At this point I would like to ask a question. It bears on the needs of the general practitioner who comes into contact with patients having mitral stenosis. They obviously would not like to have to send all their patients to a surgeon for evaluation, or to a team for evaluation before they reach the surgeon. Are there any criteria that they could use for preliminary screening, if only to determine whether a particular patient is a proper candidate for further study?

DR. LUKAS: I might mention first the patients with associated lesions. In a patient with a diastolic murmur along the left sternal border, the question arises whether there is significant aortic insufficiency. Cardiac catheterization does not help very much in this particular problem, although it can help us make fairly sure that there is a tight stenosis.

DR. READER: Is this the kind of a patient you would decide to send in for systematic evaluation?

DR. LUKAS: If I were the outside physician confronted with such a patient, I should be reluctant to make a decision without having the patient worked up fairly thoroughly before deciding on an operation.

DR. READER: How would you describe the patient about whom you might say: Here is one I ought to get right into the hospital as a good candidate for operation.

DR. LUKAS: I think Dr. Glenn defined it satisfactorily. The patient is one with unequivocal mitral stenosis, who has symptoms, or in whom it appears that the type of lesion is a progressive one and who is likely to run into trouble very shortly.

DR. READER: As I understand it, Dr. Glenn would put no age limits on surgical intervention, although he did say that the young patient is preferable.

DR. GOLD: Does operation predispose to reactivation of the rheumatic fever?

DR. GLENN: We have not been able to put our finger on the answer to this question. We have one patient, the first patient we lost early in our series, in whom we suspected that death in cardiac failure was the result of acute rheumatic fever because of the fever and the rapid pulse rate. I now have some doubt as to whether the operation has any effect.

DR. LUKAS: I am inclined to think that at operation we simply uncover the active rheumatic process which may have escaped detection previously because of the absence of the usual criteria for active rheumatic fever.

DR. O'SULLIVAN: We make it a practice not to operate upon anyone with clinically active rheumatic fever. However, the biopsy findings at operation often come as a surprise, for they sometimes turn up positive when there is no clinical support for it.

DR. LUKAS: It looks from the experience of others, for example, the review of some 450 cases by Dr. Ellis, that about 40 per cent of the patients are going to show biopsy findings positive for rheumatic activity regardless of what the criteria are for the selection of cases. The rheumatologists generally believe that if there is clinical activity operation should be withheld, but there are contrary opinions to the effect that the young patient with a tight mitral stenosis should receive the benefit of the operation even if there is active rheumatic carditis, this being kept in check with suppressive therapy before and after.

DR. READER: Dr. Lord, I wonder if we could hear about your experience with this operation and your opinions on some of the points we have been discussing.

DR. JERE W. LORD, JR.: My series is a small one, only thirty-eight patients, but we have gotten some fairly definite impressions from our experience with them. We have come to believe, as Dr. Gold mentioned, that the clinical examination is probably the most important factor in the selection of patients. Audio-visual study of the murmur as developed by Dr. Butterworth has proved to be a very useful aid. Dr. Lukas, you may recall the patient, R. H., whom you restudied for us. You may recall that your findings were suggestive of mitral stenosis. We reoperated upon her later but found instead a significant degree of insufficiency. It is noteworthy that the clinical murmurs were in keeping with the insufficiency.

In our small series we lost three patients. We could do nothing for any of these at operation. In one patient there was a very heavy deposit of calcium; in another there was marked mitral insufficiency, the valve being larger than the normal valve in an adult; and the third patient had advanced aortic stenosis.

We had all our patients come back about two weeks ago for review. What we found leads us to the conclusion that the operation was exceedingly worth while in the group of tight mitral stenosis without excessive calcification, without

insufficiency and without other organic lesions. We are now much more selective and tend to turn down many more than we accept for operation. Our mortality rate in this plan of practice will approach about 2 or 3 per cent.

DR. GOLD: I would like to ask whether in these groups of patients of Dr. Glenn and Dr. Lord there have been any who prior to the operation were in need of intensive congestive failure therapy with salt restriction, digitalis and diuretic agents but in whom after operation the circulation was sufficiently restored so that this form of treatment was no longer necessary?

DR. GLENN: Yes, we have had some of those.

DR. GOLD: Is that an exception?

DR. GLENN: I cannot give you any figures on that point; those will be forthcoming later. I can think of individual examples. The majority of these patients have to be given supportive therapy which is gradually reduced after operation and in one instance required a period of over two years.

In the matter of selection of patients for the operation, it might be well to mention that this operation is very useful in pregnant women in whom mitral stenosis has created difficulties in previous pregnancies. We have now operated upon nine patients during pregnancy. On the whole, they have done very well. I believe we have had one miscarriage.

DR. READER: Do you choose any particular stage of pregnancy for the time of operation?

DR. GLENN: The average is around five months.

DR. LUKAS: It depends, of course, on when the patients come to our attention.

DR. READER: I realize that, but it is well to know that there is no special time limit. Do you employ dicumarol therapy in relation to the postoperative emboli?

DR. GLENN: Yes, but it is not a routine postoperative procedure. Within a short period, forty-eight hours after the operation, dicumarol treatment may be used if there has been evidence of embolization before operation or clots were found in the heart at operation.

VISITOR: Are antibiotics used postoperatively in these patients routinely for any extended period of time?

DR. GLENN: Yes, but no more than for any other open chest operation. We usually carry those along with antibiotics for seven or eight days.

DR. READER: Has anyone here had experience with endocarditis developing on valves that have been fractured?

DR. GLENN: We have had none, have you?

DR. LORD: We have had none personally. In two of our patients attacks of rheumatic carditis developed which appear to have been suppressed by the prolonged use of penicillin.

DR. READER: Dr. Miscall, have you had any experience that differs from what we have heard here today?

DR. LAURENCE MISCALL: We have had one patient with a successful valvulotomy in whom endocarditis developed some months later. It was proved by blood culture and responded to penicillin.

There is one point that has pressed itself upon my attention in my experience with these patients, and that is the difficulty of predicting the reaction of any one of these patients to the surgical operation. When we first started in this field, no one was very happy about operating upon a patient except one that was in dire distress. Only later did we begin to accept other patients. It was positively amazing to us to observe how well patients tolerated the operation, very sick patients in advanced congestive failure with the liver edge down 4 or 5 fingers below the costal border and with evidence of tricuspid insufficiency. In some of these it was almost impossible to establish a degree of compensation worth speaking about prior to the operation, and in some the recovery after the operation has been very marked indeed and certainly beyond expectation.

DR. GLENN: I would like to say one word more about the anesthesia. I have talked to many people throughout the country who are doing this type of work and they have all placed much emphasis upon the need for watching the anesthesia. If they become at all apprehensive about the patient's condition, they are inclined not to proceed with the operation. I believe that in some institutions these patients receive too much anesthesia. I think I am correct, am I not Dr. O'Sullivan, that we have never found it necessary to return an anesthetized patient from the operating room before the operation for which he was scheduled?

DR. O'SULLIVAN: I think that is correct.

DR. GLENN: And I think this is due to the fact that Dr. Artusio uses a very light anesthesia in these patients.

SUMMARY

DR. HARRY GOLD: The conference this afternoon dealt with experience and elaborated points of view in regard to the operation on the mitral valve for treatment of mitral stenosis. Mitral valvulotomy has become an accepted surgical procedure with a high incidence of successful results and the mortality has been reduced to a rate well within that for other operations of similar magnitude. The discussion revolved chiefly around the experience with 130 cases at the New York Hospital. The proper selection of cases is of paramount importance, not only to reduce surgical mortality but also more significantly to increase the proportion of cases in which the operation proves successful against the hemodynamic disturbances of mitral stenosis. Satisfactory therapeutic results in about 70 per cent of the cases and an operative mortality rate of less than 3 per cent characterize the results of the group that was discussed. The extent of improvement in the patients' capacity was sufficient to call for functional reclassification (American Heart Association) in slightly less than 50 per cent, ninety patients, followed up for three months or longer.

The object of the operation is to increase the size of the mitral orifice. At the present time it seems that the chief beneficiaries of this operation are patients with mitral stenosis in whom there is evidence of progressive disability due to mechanical obstruction at the mitral valve. The operation is successful in patients with auricular fibrillation as well as in those with regular sinus rhythm, and is often helpful in those who have, in addition to mitral stenosis, a mild degree of mitral regurgitation. It is the present consensus that bacterial endocarditis, active rheumatic fever and severe mitral regurgitation are contraindications to the operation. There are some who still depend to a considerable extent on the results of cardiac catheterization for a decision on the question of selection of a patient for operation. However, there is in evidence a tendency on the part of others to place the greatest reliance on the clinical manifestations of mitral stenosis in terms of the kind of murmur; in fluoroscopic examination, the straightened left border, distended pulmonary vessels, enlarged left auricle; and a history of symptoms suggesting pulmonary overfilling or pulmonary edema. Much emphasis was placed on the importance of the anesthesia in the success of the operation, very light anesthesia combined with high oxygen intake and administered by an anesthetist trained in this special surgical field.

There was provocative discussion concerning the relative importance of physical and psychologic factors in the judgment of success or failure of the operation. These factors may work both ways, on the one hand pointing to restoration of the patient's functional capacity when this was only a matter of encouragement to the patient to use what capacity he had been previously ignoring, on the other hand pointing to failure of the operation by reason of psychic resistance to additional activity in one in whom the physical capacity of the circulation has been greatly improved by the operation.

Clinico-pathologic Conference

Joint Pains, Anemia, Neuropathy, Fever, Convulsions and Blindness

STENOGRAPHIC reports, edited by Albert I. Mendeloff, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior Medical students.

THE patient, L. K. (No. 227974), was a sixteen year old high school student, who entered the Barnes Hospital on October 9, 1953, complaining of fever, abdominal pain and weakness. She had been in good health until April, 1953, when she suffered the acute onset of general malaise and of pain and redness, without swelling, of both ankles. The pain became so intense she could not walk; while home in bed, she noted the onset two weeks later of nausea, vomiting and severe cramping lower abdominal pain. An appendectomy was performed at another hospital; the postoperative course was complicated by the occurrence of a skin rash following treatment with penicillin. After discharge from the hospital, the patient remained weak and easily fatigued until, early in June, 1953, she suddenly had a recurrence of the pain and tenderness of both ankles; in addition, both knees were similarly involved, as were the right shoulder and elbow. The lower legs and face swelled noticeably, were covered by an erythematous vesicular eruption, and there was mild fever and back pain. Because of the persistence of these symptoms, she was admitted to another hospital in August, 1953, where a profound anemia was treated with eleven blood transfusions. During this hospitalization two episodes of severe swelling of the face accompanied by headache, blurring of vision and back pain occurred. Cortisone was first administered at that time; while receiving this drug she had the acute onset of swelling of the tongue and of an eruption in the mouth, and she also had an attack of acute respiratory distress for which oxygen was administered. The oral lesion cleared after cortisone was discontinued. An electrocardiogram was said to show "evidence of rheumatic heart disease." She was discharged after five weeks in the hospital and remained at home in bed for two weeks. One week prior to her admission to the Barnes Hospital the patient began to vomit all food, and noted tingling sensations in the hands and feet. Two days prior to admission there was the sudden onset of severe abdominal pain radiating through to the back. On the day before admission an epistaxis occurred and the urine was noted to be bloody. There had been a total weight loss since April of 45 pounds.

The patient's mother had died of septicemia at the age of forty. The patient had had frequent sore throats as a child and scarlet fever at age nine. A tonsillectomy had been performed but she continued to have sore throats. It was known that she had had sinus disease for some years, had suffered from frequent frontal headaches and had had several episodes of otitis media. Her growth and development had not been affected by these illnesses.

Physical examination at the time of admission revealed the patient's temperature to be 37.7°C., pulse 130, respirations 20 and blood pressure 108/65. She was a very tall (75 inches) girl who appeared seriously ill, with evidence of marked recent weight loss. The skin was hot, dry and pale, without petechiae or ecchymoses. There were no abnormalities of the bones and joints. Periorbital edema was evident, but the eyes and fundi were normal. A blood-tinged discharge was present in the left nostril. There was no lymph node enlargement; the thyroid gland was not enlarged. The chest was symmetrical and the lungs were clear. The heart was somewhat enlarged to the left by percussion; a grade III systolic murmur was heard at the apex and at

the left sternal border. There was sinus tachycardia. The abdomen was distended and moderately tender without muscle guard or spasm. The liver edge was palpable 2 cm. below the right costal margin. The spleen and kidneys were not felt. Bowel sounds were hypoactive, but the abdomen contained no free fluid. The extremities were weak, the peripheral pulses were good, the cranial nerves were intact and deep tendon reflexes physiologic. There was a glove and stocking distribution on hands and feet of hyperesthesia to pain and to light touch.

The laboratory examinations were as follows: red blood cell count, 2,880,000; hemoglobin, 7.8 gm. per 100 ml.; white blood cell count, 5,000; differential: segmented neutrophils, 58 per cent; stab forms, 4 per cent; lymphocytes, 37 per cent; eosinophils, 1 per cent. Platelets appeared adequate; there was marked hypochromia and anisocytosis. Urinalysis: specific gravity, 1.010; pH, 5.0; albumin, 4+; sugar, negative; centrifuged sediment: red blood cells, 6 to 10 per high power field, white blood cells, 30 to 35 per high power field. Stool: guaiac positive. Blood cardiolipin test, negative. Blood chemistry: non-protein nitrogen, 25 mg. per cent; sugar, 70 mg. per cent; sodium, 141 mEq./L.; potassium, 2.4 mEq./L.; carbon dioxide combining power, 30 mM/L.; chloride, 102 mEq./L.; calcium, 9.1 mg. per cent; phosphorus, 3.8 mg. per cent; total proteins, 4.9 gm. per cent; albumin, 3.3 gm. per cent; globulin, 1.6 gm. per cent; cholesterol, 111 mg. per cent. Porphobilinogen test: negative; L.E. preparations (five), negative; clotting time (Lee-White method), 6.5 minutes; platelet count, 200,000 per cu. mm. First strength PPD and histoplasmin tests, negative; bone marrow studies: "generally hypercellular marrow showing normoblastic hyperplasia. Myeloid and megakaryocytic elements appeared normal. No L.E. cells were seen on an incubated preparation." Antistreptolysin "O" titer, less than 25 units. Roentgenogram of the chest: minimal cardiac enlargement. Roentgenogram of abdomen: marked distention of small and large bowel. Electrocardiogram: sinus tachycardia.

The patient's hospital course was characterized by changes in mental status and disturbed function of peripheral nerves. She was initially treated with bed rest, parenteral fluids and analgesics. Her anemia was partially corrected with transfusions of washed red blood cells. On the fourth hospital day a urine culture showed a heavy growth of coliform organisms, and on the following three days she developed a sore throat with cervical adenopathy and high fever. Erythromycin and streptomycin administration at this time resulted in a prompt disappearance of symptoms and fever. Paresthesia in arms and legs increased, she had frequent periods of confusion and lumbar puncture was performed on the ninth day. The fluid was clear, under slightly increased pressure and contained protein, 93 mg. per cent. On the thirteenth hospital day her blood non-protein nitrogen had risen to 40 mg. per cent, although her other blood electrolytes were remarkable only for a slight decrease in carbon dioxide combining power and a slight increase in chloride concentration. She had persistent albuminuria and hematuria; red blood cell casts were seen repeatedly from the twelfth day on. A four-day course of ACTH was begun on the eighteenth hospital day; this was changed to oral cortisone without evidence of therapeutic response. There was a gradually ascending motor paralysis and sensory loss, although severe pain persisted and was unaffected by massive doses of cobalamin and of BAL. The blood pressure gradually rose during cortisone therapy, as did the white blood cell count; on the thirty-fourth hospital day the patient had a leukocyte count of 24,000, developed severe vertigo and nystagmus, complained of headache and nausea, then exhibited a generalized convulsion. At this time her blood pressure was 170 mm. Hg systolic. Following the convulsion a right homonymous hemianopsia was detected. Forty-eight hours later she had another generalized seizure and thereafter was completely blind. Other cranial nerves exhibited no abnormalities.

Pulmonary congestion then ensued and was partially controlled by intravenous digitalization and by oxygen. The temperature rose to 38.7°C., chlortetracycline was added to the intravenous fluids, and the patient became somewhat more responsive. Her blood pressure again rose and remained at 180 mm. Hg systolic, associated with persistent tachycardia. ACTH was again begun, with hexamethonium being administered concurrently for control of the hypertension. On the thirty-ninth hospital day a blood culture grew out Staphylococcus albus in the broth only. On the forty-first hospital day she had papilledema on the left, and her blood chemistry data were as follows; non-protein nitrogen, 25 mg. per cent; sodium, 140 mEq./L.;

potassium, 4.1 mEq./L.; chloride 101 mEq./L.; carbon dioxide combining power, 32.9 mM/L. A lumbar puncture on the forty-second hospital day yielded clear fluid under an initial pressure of 690 mm. of water. The cell count was 109 cells without acid, 13 with acid. Red cells seen were crenated. The protein concentration was 73 mg. per cent. Cultures: no growth. Two days later, because of increasing headache, the puncture was repeated. Eighteen ml. of xanthochromic fluid under an initial pressure of 700 mm. water were removed. The closing pressure was 300 mm. water. Headache returned one hour after the lumbar puncture, and persisted until the forty-fifth day, when the patient began to have labored respirations, falling blood pressure and cyanosis. Attempts to control these symptoms were unavailing and she expired on November 25, 1953.

CLINICAL DISCUSSION

DR. VIRGIL SCOTT: The lengthy protocol adequately describes the problem presented by this patient, and if Dr. Elliott will discuss the x-ray examinations, we should be in possession of all the necessary clinical information.

DR. GLADDEN V. ELLIOTT: This patient had an examination of the chest and abdomen the day after hospital admission. There was a minimal but rather definite cardiac enlargement in both the transverse and anterioposterior planes. The lung fields themselves showed prominent vascular markings bilaterally, which tended to become somewhat indistinct in the periphery. The lung fields otherwise were thought to be clear. The slight increase in cardiac size and the prominence of vascular markings with the terminal fuzziness were compatible with pulmonary congestion. Films of the abdomen showed only a single gas-filled loop of jejunum and some gas throughout the colon. The soft tissues were interpreted as within normal limits. Since gas is present throughout the intestinal tract, obstruction was not thought likely. The kidney shadows were obscured by the gas; the liver was not much enlarged and no splenic shadow was seen.

DR. SCOTT: From the clinical information available it is clear that several organ systems were involved by this process. It may be of some help at the onset to attempt to decide whether this is a disease which arose *de novo* in multiple organ systems at the same time, or whether, on the other hand, the disease process originated in one organ at the beginning, and subsequently became disseminated to involve other structures. The role of the heart in this case seems important, and the protocol provides evidence suggesting that a beta hemolytic streptococcus might have been one of the important causes of her illness. You will recall that in the patient's past history there was a history of scarlet fever; she had had frequent sore throats, otitis media and joint pains. Now, Dr. Graham, would you comment on this aspect of the disease process?

DR. DAVID T. GRAHAM: My feeling is that she had rheumatic heart disease with superimposed subacute bacterial endocarditis, and that many of the disseminated manifestations may represent embolization from an involved mitral valve.

DR. SCOTT: Is there any other comment with reference to the heart? You will recall that the antistreptolysin titer was reported as being less than 25 units. Is that of any significance, Dr. Glaser?

DR. ROBERT J. GLASER: It does not rule out rheumatic fever. About 80 per cent of patients who have a streptococcal infection develop an antistreptolysin "O" response. The evidence suggests that patients within that group who are going to develop rheumatic fever have a more vigorous response than do the non-rheumatics. In an individual case, of course, the titer has much less value than in a series of a thousand cases, but I would say the absence of any antistreptolysin "O," which is essentially what this test value means, would certainly militate against the diagnosis of acute rheumatic fever.

DR. SCOTT: It does not militate against the diagnosis of chronic rheumatic heart disease?

DR. GLASER: No. Patients who have rheumatic heart disease following rheumatic fever occurring many years before may not have any antistreptolysin in their blood. The response obviously is to the streptococcal infection and has nothing to do specifically with rheumatic heart disease except insofar as rheumatics seem to respond more dramatically to acute streptococcal infection than do non-rheumatics.

DR. SCOTT: I am not entirely taken, Dr. Graham, with your suggestion that this is subacute bacterial endocarditis. The patient had relatively little fever. She had an essentially normal or low white count on admission and still had been ill for some six months prior to that time. The spleen was not felt to be enlarged at

any time. One blood culture was reported as showing Staphylococcus albus in broth only. What is the significance of this?

DR. CARL G. HARFORD: Since organisms grew only in nutrient broth, if there were bacteria in the patient's blood they were there in extremely small amounts, less than one organism for every 10 ml. of blood. Staphylococcus albus is a common contaminant both from the air and from the skin, so that this evidence is not to me indicative of bacterial endocarditis. However, I was struck by the large number of features of this case which were consistent with a diagnosis of bacterial endocarditis. Certainly these patients sometimes do not have fever or any change in the white count.

DR. SCOTT: Do you have any comments, Dr. Taussig?

DR. BARRETT TAUSSIG: My feeling is that all these symptoms, from the brain down to the abdomen, are due to embolization. It is most extraordinary that she never showed any peripheral manifestations of embolus.

DR. SCOTT: Let us now consider the kidneys, which are also organs involved in diseases caused by the beta hemolytic streptococcus. The patient had edema, not only dependent edema of the lower extremities, but periorbital edema as well. The urine contained large amounts of albumin, large numbers of red blood cells, and red blood cell casts were seen repeatedly in the sediment. What is going on in the kidneys?

DR. LILLIAN RECANT: I wish I could tell you, Dr. Scott. The combination of periorbital edema and peripheral edema in renal disease occurs in either of two circumstances, first, during an acute nephritis, when presumably one of the mechanisms for edema formation is the toxic permeability factor or, secondly, in the nephrotic syndrome when there is a very low serum albumin. Now, in this particular patient there is very little indication that she had an acute renal process, at least at the beginning, when she came in with the severe albuminuria and had manifestations of periorbital edema and peripheral edema; in the second place, her serum albumin is not at a level sufficiently low so that we can call this a nephrotic syndrome. It would, therefore, seem to me that the periorbital edema is probably not related to the renal disease. With regard to the type of renal disease present, E. coli organisms were cultured at one point in very large numbers, and there were very significant numbers of white blood cells found in the urine, making it likely that she had a kidney infection, probably pyelonephritis. The presence of red cell casts is usually a very significant finding in renal disease. It is associated either with the malignant phase of nephrosclerosis or with acute glomerulonephritis, and it would seem to me that in all probability she had several disease processes going on in the kidney: one pyelonephritis and, secondly, a more acute phase of her general disorder, whether that be subacute bacterial endocarditis or one of the collagen diseases.

DR. SCOTT: You brought up the question of so-called collagen disease. Will that produce these changes in urinary sediment?

DR. RECANT: Certainly in lupus and polyarteritis one can find very marked hematuria and albuminuria. This degree of pyuria would be relatively uncommon in either disease, and would have to be atttributed to co-existent infection of the kidney.

DR. SCOTT: The house staff diagnosis was chronic glomerulonephritis.

DR. MELVIN GOLDMAN: I cannot agree with that diagnosis. The predominant lesion in the kidney must have been a glomerulitis of some type, and certainly collagen disease may well have caused it.

DR. SCOTT: It is of interest that recent investigators in this field have emphasized that in diseases characterized by necrosis of arteries or arterioles the urinary sediment may contain red blood cells, red blood cell casts, oval fat bodies, fatty casts and protein, often in the same urinary specimen. It is quite usual to find these abnormalities individually in various types of renal diseases, fatty casts in the nephrotic stage of glomerulonephritis, red cell casts in acute glomerulonephritis, but in the usual forms of those diseases primarily affecting the kidneys it is very unusual to find all these abnormalities in the same urinary specimen. As I understand these recent studies, it is still not clear that one can attribute the various renal disturbances in collagen diseases to one underlying renal vascular lesion, or to a number of different types of well recognized diseases of the nephron, which occur in a haphazard sequence during the course of the diseases. In any case, the urinary findings in this case do not help us in distinguishing between lupus erythematosus and polyarteritis.

Dr. Mendeloff, the gastrointestinal tract may have been involved in this patient. She had a great deal of abdominal pain. There was per-

sistent nausea and vomiting and several of the stools were guaiac positive. Can we differentiate the process in the abdomen any further?

DR. ALBERT I. MENDELOFF: Dr. Scott, I don't find anything in the protocol which enables me to localize these lesions either physiologically or topographically. Severe abdominal pain is, of course, found in acute rheumatic fever, but persistent and recurring pain, abdominal or otherwise, is one of the most common features of polyarteritis. Was this pain constant and well localized?

DR. WILLIAM PERRY: This pain varied from place to place, and did at one time radiate through to the back. It was a severe pain, sometimes colicky, sometimes not.

DR. MENDELOFF: That would be quite compatible with the pain complained of by patients with polyarteritis. My experience with lupus is not very great, but I have seen some patients with lupus who had chest pain and vague abdominal pain. I do not remember any lupus patient in whom severe colicky abdominal pain was a feature. Polyarteritis, of course, classically produces necrotic lesions in the gallbladder, liver and mesentery, which presumably give rise to the severe pain complained of by these patients. Polyarteritis in this case would then be a more likely diagnosis than lupus or acute rheumatic fever.

DR. SCOTT: Dr. Perry, certainly lupus was strongly considered while this patient was in the hospital. Would you comment on the features of her illness which go along with that diagnosis.

DR. PERRY: She was a young, white female, suffering from a disease involving multiple systems. At one time she had a skin rash, possibly related to penicillin. She had joint and muscle involvement, signs of degeneration of both her peripheral and central nervous system, and cardiac and renal damage, all of which would fit the clinical picture of lupus. The severity of these lesions of the central nervous system and the peripheral neuropathy might, however, lead one away from lupus to some extent.

DR. SCOTT: This patient received adrenal steroid treatment on several occasions. When first she was given cortisone there was no elevation of blood pressure, and she was placed on 400 mg. of cortisone a day. There was a gradual rise in her blood pressure to levels of around 180 systolic, 110 diastolic. Following this rise in blood pressure she began to have convulsions. Would you discuss, Dr. Daughaday, the occurrence of hypertension and convulsions in persons who are receiving adrenal steroids.

DR. WILLIAM H. DAUGHADAY: Convulsions are a well recognized complication of cortisone and ACTH therapy, and seem likely to arise when one is treating diseases in which actual brain damage has occurred. The occurrence of convulsions is one of the common complications of cortisone therapy in treating lupus and, in fact, collagen diseases generally; in the treatment of less serious diseases, convulsions rarely occur. Perhaps cortisone lowers the threshold for convulsions and any pre-existing brain damage thus becomes more evident. With regard to her hypertension, it is possible that the cortisone had little influence on its progress, which was closely related to her underlying renal disease. It is impossible to tell how much hypertensive effect was due to cortisone and how much to the underlying renal disease.

DR. SCOTT: In that respect, her blood pressure fell later in the course of her illness. She was taken off cortisone. She was then treated with ACTH and was given hexamethonium. Finally the hexamethonium became unnecessary, and terminally her blood pressure fell to low levels. With regard to your preliminary remarks about cortisone seeming to have more convulsive effects in patients who clearly have central nervous system disease, you will recall from the protocol that the patient had been confused, and that at the time of the initial examination the total spinal fluid protein was slightly elevated.

DR. SAMUEL BUKANTZ: Before you go on to the next phase, I wonder whether any effort had been made to discover what had been seen at the laparotomy elsewhere.

DR. SCOTT: There was no such information in the hospital record. The patient began to develop peripheral neuropathy shortly prior to entry. The involvement of peripheral nerves became exceedingly severe, and prior to the onset of her convulsions had progressed so that she was practically unable to move any extremity. You will recall that after large doses of cortisone were given she had a convulsion following which an homonymous hemianopsia was found. She then had another convulsion and following this was totally blind. Dr. Levy, would you discuss, (1) the involvement of the peripheral nerves and (2) what was going on in the central nervous system.

DR. IRWIN LEVY: The question was asked as to whether this peripheral nervous system

involvement was compatible with polyarteritis. She had a painful diffuse peripheral neuropathy, involving both sensory and motor systems, a picture often seen in patients with polyarteritis. As far as other possibilities are concerned, some of the neuropathies following infection can resemble this, but the general course of the disease was not very characteristic of other types of infection that could give peripheral neuritis. We thought of porphyrinuria, and tried to rule that out by the usual urine studies; arsenic poisoning seemed unlikely on the basis of urinary arsenic concentrations, and by the negative response to BAL. She became steadily worse, and then began to show some changes in the central nervous system, vertigo, for example, and finally convulsions. These were not of the usual mild type seen with ACTH or cortisone. In this particular patient there were two generalized convulsions, and each was followed by hemianopsia on the opposite side; in other words, she had first a convulsion followed by a right hemianopsia, and then a convulsion preceding the onset of complete blindness. These profound changes in her clinical picture seemed to indicate hemorrhage in the brain in the occipital lobes, rather than a diffuse change in electrolyte balance or water metabolism. I believed she had focal disturbances in her brain, but I could not differentiate between polyarteritis and lupus as the underlying cause.

Dr. Scott: I have taken the liberty of trying to summarize the information that is available in respect to the differentiation of lupus and polyarteritis. In Table 1 there are four groups of patients; the table summarizes published experience with forty-four, sixty-two and thirty-four cases, respectively, of lupus erythematosus; the polyarteritis nodosa material is from 177 cases described by Harris in 1939. Symptoms that this patient exhibited which are of about equal frequency in both conditions are fever, convulsions, nausea and vomiting, proteinuria, hematuria and edema. Of the group of symptoms occurring a little more frequently in polyarteritis nodosa, this patient had weakness, weight loss, joint pains and anemia. She did not have generalized lymphadenopathy nor a positive serologic test for syphilis. Leukopenia of 5,000 white cells or less, change in the serum proteins with elevated serum globulins, the presence of L.E. cells and thrombocytopenia are all more common in lupus than in polyarteritis. In respect to the skin rash, this is of course common in lupus. In polyarteritis, purpura is described in 27 per cent of those 177 patients. Of course, this patient did not have many of these features. The white count initially was 5,000. She did not have a skin rash while under observation. The serum proteins here were low, but there was no increase in serum globulin. L.E. cells were not found in five examinations of the peripheral blood or in one examination of material aspirated from the bone marrow. Neuritis is described in 49 per cent of the patients with polyarteritis, with sensory involvement in 34 per cent. I would like to point out, however, that there are several, if not a number, of patients, with disseminated lupus in whom the same phenomenon has been described. There are at least four or five such patients in the literature with decidedly the same type of peripheral neuropathy including sensory loss. Hypertension is, of course, more common in polyarteritis, as is leukocytosis, and in some types of polyarteritis there is also an eosinophilia. Now, so far, we have had three diagnostic possibilities suggested: subacute bacterial endocarditis, lupus erythematosus and polyarteritis.

Dr. Recant: Dr. Scott, do you think that the failure of a patient to show a really good response to tremendous doses of cortisone and ACTH would influence you in one direction or the other with regard to making a diagnosis? Specifically would you anticipate that if this were one of these two collagen diseases there would have been some evidence of response?

Dr. Scott: Dr. Alexander, would you care to comment on this?

Dr. Harry L. Alexander: I think it is a matter of the dosage. Dr. Rose in Montreal gives 3 gm. of cortisone the first day in these desperate cases, and 400 mg. to him would be a small dose. I would very much favor polyarteritis here for two reasons. In the first place, if this were lupus one should have seen L.E. cells after five of these careful examinations. Secondly, the peripheral neuritis, as you mention, may occur in lupus, but it is very characteristic of polyarteritis, and the abdominal pain leading to appendectomy would emphasize that. There is one reservation, and that is the initial leukocyte count of 5,000, which is very low. There are undoubtedly instances in which the differentiation is practically impossible.

Dr. Glaser: It is my impression that that may be more true in female patients than in males because polyarteritis is, of course, more com-

mon in males, whereas lupus is more common in females.

DR. HARFORD: I would like to ask whether anybody knows whether cortisone has any effect on the L.E. test. In other words, might these results be false negative tests due to the fact that the patient received cortisone before she entered the hospital?

DR. SCOTT: There are statements in the literature that L.E. cells have been noted to disappear while cortisone is being administered and to reappear after cortisone is discontinued. Does anyone have any further information in respect to this point?

DR. KEITH WILSON: Last summer we had a similar problem in a young Negro who had

TABLE 1

COMPOSITE SHOWING PERCENTAGE OF PATIENTS EXHIBITING SIGNS OR SYMPTOMS LISTED ON THE LEFT

No. of Patients	Lupus Erythematosus			Polyarteritis Nodosa
	Jessar* 44	Dubois† 62	Shearn‡ 34	Harris§ 177
Fever	95	97	100	81
Convulsions	7	30	15	11
Nausea and/or vomiting	18	40	50	33
Proteinuria	70	..	62	65
Hematuria	.....	..	35	48
Edema				
Orbital	12	..	...	.....
Pedal	25	..	53	.....
Abdominal pain	22	42	35	56
Neuritis	"rare"	..	...	49
Hypertension	18	..	32	53
Leukocytosis	31	..	...	73
Eosinophilia (4% or more)	...	..	...	33
Weakness	100	..	97	45
Weight loss	100	82	74	44
Joint pain	77	90	85	34
Lymphadenopathy	37	42	68	11
Anemia	95	78	97	48
STS positive	28	33	19	8
Pleuritis (or effusion)	39	60	24	.....
Pericarditis	23	44	18	.....
Peritonitis (or ascites)	...	24	15	.....
Hepatomegaly	29	34	44	"few" to "many"
Splenomegaly	27	1	41	"rare"
Raynaud's phenomena	16	35	6	.....
Photosensitivity	...	40	58	.....
Skin rash	68	84	91	Purpura 27 Nodules 25 Other 4
Leukopenia—5,000 or less	70	68	74	
Serum globulin elevated to 3.0 gm. %	82	28	62	
L.E. cells	...	69	94	
Thrombocytopenia	...	10	31	

* JESSAR, R. A., DAMONT-HAVERS, R. W. and RAGAN, C. Natural history of lupus erythematosus disseminatus. *Ann. Int. Med.*, 38: 717, 1953.

† DUBOIS, E. L. The effect of the L.E. cell test on the clinical picture of lupus erythematosus. *Ann. Int. Med.*, 38: 1265, 1953.

‡ SHEARN, M. A. and PIROFSKY, B. Disseminated lupus erythematosus. Analysis of thirty-four cases. *Arch. Int. Med.*, 90: 790, 1952.

§ HARRIS, A. W., LYNCH, G. W. and O'HARE, J. P. Periarteritis nodosa. *Arch. Int. Med.*, 63: 1163, 1939.

typical lupus erythematosus, confirmed at autopsy, in whom at no time were L.E. cells found. He received no cortisone at first, and the cells were searched for. Opinion at that time was that patients who have had cortisone or ACTH therapy probably still exhibit the L.E. phenomenon but, as anyone who has looked for it will realize, sometimes the reaction is very difficult to identify. Certainly the absence of L.E. cells in this patient does not necessarily rule out the diagnosis of lupus, although I would agree that the diagnosis in this particular instance seems to me to be more likely to be polyarteritis.

DR. SCOTT: On a show of hands from the audience, polyarteritis nodosa seems to be the popular diagnostic choice in this case.

PATHOLOGIC DISCUSSION

DR. JOHN C. SUTHERLAND: The anterior layer of the pericardium was extremely edematous and thickened to as much as 8 mm. The pericardial sac contained 175 ml. of clear fluid, but the visceral and parietal layers were smooth and glistening. The heart weighed 360 gm. and was not considered to be much enlarged, as the patient was 6 feet, 3 inches tall. The valve leaflets and cusps were thin and all endocardial surfaces were smooth and glistening. The lungs were light and weighed only 760 gm. There was a distinct, diffuse brown coloration of the parenchyma apparent through the pleura and on cut surfaces. The liver showed a dark red accentuation of the central areas indicative of moderate congestion. The spleen was small, weighed 100 gm. and showed prominent follicles. An ulcer which measured 1 cm. in diameter was present on the posterior wall of the first part of the duodenum. It extended through the muscularis and was closely applied to the underlying pancreas, but there was no spillage of intestinal contents into the peritoneum. There were petechiae and ecchymoses in the mucosa of the small intestine. The cecum was distended and on its mucosa there were numerous shallow ulcers, the craters of which were filled with fibrinopurulent material. The kidneys were enlarged to weights of 180 gm. and 210 gm. The cortices were swollen and pale, and on the exposed capsular surfaces the vessels were prominent. A slight fine granular scarring was present over the entire cortex and occasional dark dots were interpreted grossly as petechiae. In each occipital lobe of the brain there was a hemorrhage measuring 3 or 4 cm. in greatest diameter. The hemorrhages were within the white matter and compressed the posterior tips of the lateral ventricles without rupturing into the ventricular system. The vessels of the brain showed no gross evidence of any pathologic change.

DR. DAVID E. SMITH: The findings of the autopsy at the time the gross examination was completed presented a rather confusing array of lesions involving the kidneys, pericardium, lungs, brain, duodenum and cecum, but not the heart. It was necessary to prepare an unusually large number of microscopic sections before sufficient evidence was at hand to enable us to believe we understood what had happened in this case.

Figure 1 is an illustration of a section from the pancreas. It shows a relatively large artery in which a segment of the wall in the upper part of the photograph has been converted into a fuzzy, eosinophilic, essentially structureless mass. This is fibrinoid necrosis; it is to be noticed that it is segmental and involves only the inner layers of the artery, but that in the surrounding adventitia there are a few inflammatory cells. This is an acute and typical, but not at all florid, lesion of polyarteritis nodosa. Figure 2 shows one of the few other arteries in which some damage has occurred. It represents a considerably higher magnification of a very small artery in the capsule of the adrenal. There is thickening of the intima to a degree that would be quite unusual for a person sixteen years of age, and there is also a cellular infiltrate in the adventitia. These two changes were interpreted as indicative of an inflammation of the blood vessel wall. This lesion seems to be quite chronic or even healed, while the first lesion was more acute and active because it shows fibrinoid necrosis. It is rather disappointing to go through thirty or forty sections of the viscera and not find more vessels that are actively involved, but these two are quite characteristic and compatible with a diagnosis of polyarteritis nodosa.

The kidney in Figure 3 shows some very interesting changes which are strong supporting evidence for this diagnosis. Many of the glomeruli are obliterated by fibrous tissue and there is a reactive hypertrophy of the endothelium over them. In a large number of glomeruli, like the three in the illustration, half or more of the glomerulus was converted to scar tissue. Other glomeruli were practically normal. This lesion looked like healed focal embolic glomerulo-

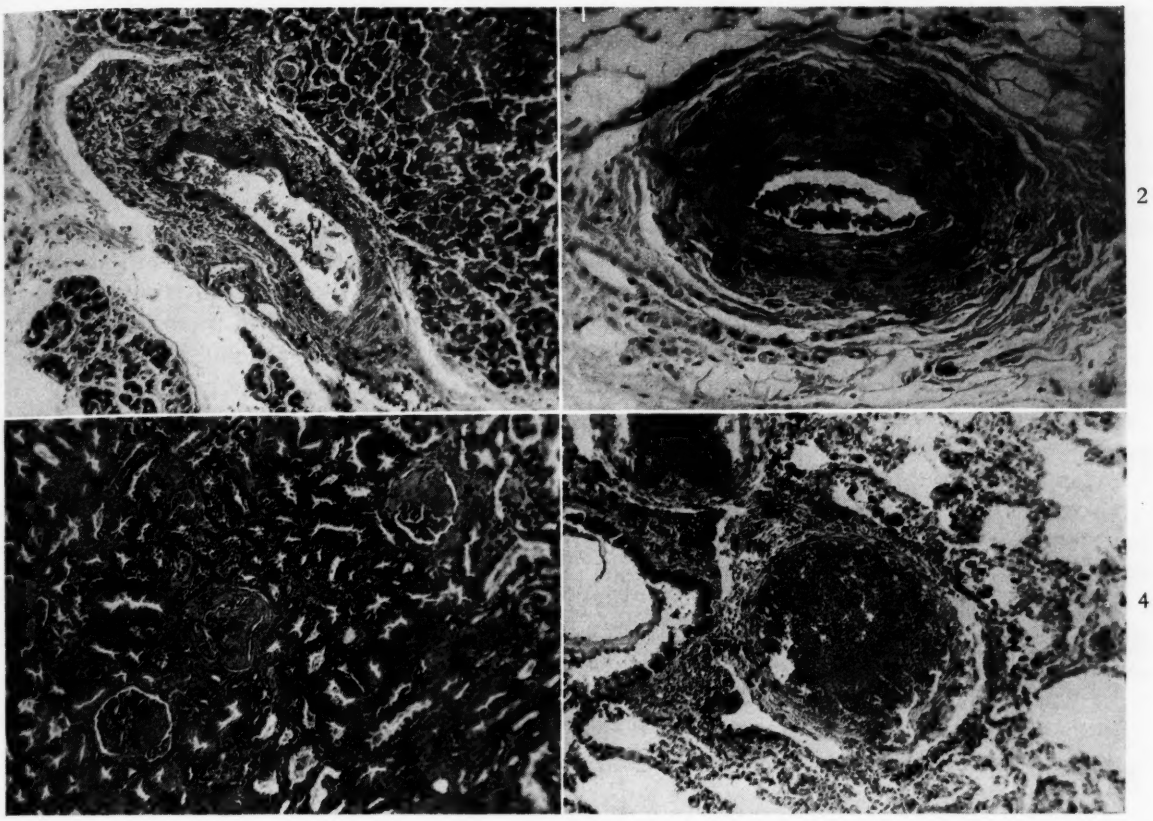

FIG. 1. An artery in the pancreas showing segmental fibrinoid necrosis of the media with inflammation and fibrosis in the adventitia. There is also a slight extension of inflammation into the interstitial tissue of the pancreas.

FIG. 2. A small artery in the capsule of the adrenal showing an unusual degree of fibrous thickening of all parts of the wall and a few remaining chronic inflammatory cells in the adventitia. This is interpreted as a suppressed or healed lesion of polyarteritis nodosa.

FIG. 3. The kidney showing segmental fibrous scars in the glomeruli with very little changes in the tubules or interstitial tissue. This lesion is considered to be a result of the acute lesion described by Davson, Ball and Platt as occurring in some case of polyarteritis nodosa. The progression to fibrous tissue is probably the result of the effectiveness of modern steroid therapy.

FIG. 4. The lungs showing a small thrombus in a pulmonary artery and large masses of hemosiderin lining the walls of alveoli. There is practically no evidence of chronic passive congestion or fibrosis of the interstitial tissue of this lung.

nephritis, but there was no evidence of active or healed bacterial endocarditis in the heart. There was also relatively little evidence of tubular damage or interstitial fibrosis. Davson, Ball, and Platt[1] in 1948 described a number of cases of polyarteritis in which there was acute segmental or lobular necrosis of glomeruli in the kidneys. They commented that many other cases have probably masqueraded in the literature under various names, such as atypical glomerulonephritis, or focal embolic glomerulonephritis without bacterial endocarditis. However, by multiple sections of the kidney and other viscera they were able to find lesions that established the diagnosis of polyarteritis nodosa. The described cases were all acute and without transformation of the glomerular lesions to fibrous tissue, but these cases antedated effective steroid therapy for this disease. Since it has been well shown that intensive ACTH and cortisone therapy can prolong the course and almost completely suppress the activity of the lesions of polyarteritis, it seems quite logical to accept this renal lesion as a healed stage of that described by Davson and his co-authors. Combined with the account they give of the extent to which typical vascular lesions had to be sought before the nature of their cases was apparent, the segmental glomerular scars and rare but characteristic arterial lesions in the

[1] DAVSON, J., BALL, J. and PLATT, R. The kidney in periarteritis nodosa. *Quart. J. Med.*, 17: 175–202, 1948.

present case indicate that it differs from theirs only by the influence of present-day therapy.

Frozen sections of the peripheral nerves stained with the Sudan stain show a random distribution of neutral fat in the myelin sheaths, indicative of fatty degeneration accompanying active peripheral neuropathy. This lesion in polyarteritis has been correlated in many cases with involvement of the small arteries of the nerves, and is a peripheral Wallerian degeneration. Unfortunately, arterial lesions in the nerves in this case were as undemonstrable as they were in most of the viscera, and not at all proportional to the extent of the degeneration in the nerves. Sections of the brain showed the acute hemorrhages in the occipital lobe, but no evidence of primary vascular involvement, although it is suspected that the bleeding must have arisen from diseased vessels affected in the same manner as those in the pancreas.

The lungs presented apparently a separate and interesting problem. There were multiple recent thrombi in small branches of the pulmonary artery. By their composition these were considered to be probably emboli, but they seem to be of little importance from either the clinical or pathologic standpoint. Many of the alveoli, however, contained large macrophages filled with iron pigment, as shown in Figure 4. These were more numerous than one would expect with chronic passive congestion of the lung alone, the changes of which were practically absent in the remainder of the parenchyma or vessels of the lung. There has been described a syndrome of primary pulmonary hemosiderosis[2] of which they may have been an early example. It is usually a disease of children and often leads to extensive scarring and disruption of elastic tissue in the lung, in contrast to the simple deposition of hemosiderin in the alveolar walls in the present case. The pigment presumably arises from multiple small hemorrhages. The disease runs a course of relapsing acute episodes. The only event in this patient's history that seems compatible with the clinical histories of cases of primary hemosiderosis of the lung is the attack six months before admission and two weeks after the onset of joint pain, in which the patient was fatigued and prostrated and then several weeks later became severely anemic. Neither the syndrome nor the lesions of pulmonary hemosiderosis are recognized consequences of polyarteritis nodosa, so these autopsy findings in the lung are best interpreted as an incidental early case of hemosiderosis which shows only alveolar hemosiderin, without the chronic and secondary damage to the lung that results in the typical nodular roentgenographic picture.

Finally, the intestinal tract contained an ulcerating pseudomembranous colitis in the ascending colon, the microscopic appearance of which was typical of the mucosal infection, usually terminal, due to invasion by a bacterial organism, often proteus or a staphylococcus. In this case, postmortem blood cultures grew out Proteus vulgaris, suspected of having been derived from the colon. Microscopic sections of the ulcer in the duodenum and of the remainder of the gastrointestinal tract did not demonstrate vascular lesions, although we cannot refrain from speculating that such might have been present to initiate the ulcer before being modified by the intensive hormonal therapy given this patient.

Final Anatomic Diagnoses: Polyarteritis with acute segmental arteritis in the pancreas and chronic arteritis of small arteries in the capsule of the adrenal; lobular and complete scars in the renal glomeruli; acute degeneration of myelin in peripheral nerves; acute ulcer of the posterior wall of the first part of the duodenum with perforation; diffuse hemosiderosis of the lungs.

[2] WYLLIE, W. G., SHELDON, W., BODIAN, N. and BARLOW, A. Idiopathic pulmonary hemosiderosis. *Quart. J. Med.*, 17: 25–48, 1948.

Case Reports

Streptococcus Lactis Isolated from a Patient with Subacute Bacterial Endocarditis*

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THE identification of streptococci from cases of subacute bacterial endocarditis is of importance for at least two reasons. First: With the aid of serologic or biochemical identification the portal of entry of the causative organism can sometimes be definitely or, more often, provisionally identified. Second, when subacute bacterial endocarditis recurs successful identification of the microorganism bears on the question of whether the disease is a true reinfection or whether, as happens more frequently,[1] it is due to the organism first responsible. Several attempts at serologic classification of "viridans" streptococci cultured from teeth and throats of patients with subacute bacterial endocarditis have been carried out.[1–3] Most of these strains can be grouped serologically. The groups do not, however, usually correspond to the Lancefield groups of beta hemolytic streptococci; indeed, most streptococci implicated in subacute bacterial endocarditis fall into other serologic groups.

The case to be described is that of a young man whose subacute bacterial endocarditis was caused by Streptococcus lactis, Lancefield Group N. In so far as we are aware, this is the first reported case of subacute bacterial endocarditis caused by this organism, although Wagner in 1944 described two instances of human infection with Strep. lactis. One of his patients had a blood stream infection, the other a local infection[4] but neither was diagnosed as subacute bacterial endocarditis.

CASE REPORT

The patient was a twenty-one year old college student who during the two weeks prior to admission to the hospital had noted painful swellings of both ankles and severe pain in his back. He fatigued easily during this period and had intermittent fever. There had also been anorexia and weight loss. During these weeks the patient was studying for his final examinations in college and sometimes picked at the gum at the base of a first molar tooth, known to be non-vital for several years following root canal work, which often caused bleeding. During this period the patient ate large amounts of sour cream, containing Streptococcus lactis, which is normally an innocuous inhabitant of cream. The patient had had no known attack of acute rheumatic fever but at the age of twelve an apical systolic murmur was detected which had not previously been heard. This murmur had persisted unchanged over the years.

Physical examination on admission showed that the patient was febrile and acutely ill. A long, loud, rough systolic murmur was heard at the apex. This murmur was transmitted both to the axilla and to the base. No diastolic murmur was heard. The cardiac rhythm was regular. Blood pressure was 110/80. There was bilateral posterior cervical lymphadenopathy. The spleen was not palpable. The only petechial lesion found at this time was a small splinter-shaped hemorrhage on the distal pad of the right index finger. The urine obtained on admission of the patient contained 5 to 10 red blood cells and many white blood cells per high power field. Daily blood cultures were obtained following admission. Because the patient was admitted with a provisional diagnosis of rheumatic fever, a therapeutic trial of salicylates was instituted until bacteriologic examination of the blood in search of a suspected microorganism could be completed. Salicylates were given for five successive days but, in spite of blood salicylate levels of 200 gamma/cc., the patient had daily

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temperature elevations as high as 102°F. On the sixth and seventh hospital days petechiae appeared on the thenar eminence of the left hand and on the ball of the right foot. On the sixth hospital day streptococci were observed growing in blood cultures taken on the first and second days.

Penicillin and dihydrostreptomycin therapy was started on the seventh hospital day: 1,000,000 units of penicillin every three hours, and 0.5 gm. of dihydrostreptomycin every six hours were given intramuscularly. From the third day of antibiotic treatment the patient's temperature remained normal. This intensive antibiotic treatment was continued for twenty-two days by which time many blood cultures, to which penicillinase had been added, were sterile.

Convalescence in the hospital for a month following discontinuance of antibiotics was uneventful and without any clinical or bacteriologic evidence of subacute bacterial endocarditis. Repeated blood cultures were sterile. During this time two teeth were extracted without clinical disturbance. One of these teeth was the dead right first molar beneath which a small apical abscess was found. The socket was not cultured.

At the time of discharge from the hospital there was no change in the loud, long, rough systolic murmur originally heard at the apex and transmitted to the left axilla and the base of the heart. During the four-month interval following discharge from the hospital there was slight cardiac enlargement with development of left atrial prominence but this eventually returned to normal.

BIOLOGIC STUDY OF THE STREPTOCOCCUS ISOLATED

The streptococcus isolated from all blood cultures grew poorly on blood agar even when incubated anaerobically, although growth was better in all media under anaerobic than aerobic conditions. The organism grew well in thioglycollate broth, forming long chains typical of "viridans" streptococci. There were several characteristics that led to the suspicion that this organism might be a strain of Strep. lactis. These were poor growth on blood media, anaerobiosis, curdling of litmus milk, and the cheesy smell of the freshly grown cultures on sucrose agar plates.

A strain of Strep. lactis was isolated from a sample of each of the three brands of sour cream which this patient ate in quantity prior to his hospitalization. One of these strains had growth characteristics very similar to those of the streptococcus isolated from the blood stream. The strain obtained from this brand of sour cream, as well as one of those obtained from the patient and a known laboratory strain of Strep. lactis, were compared for their ability to ferment a series of test substances. All three were mannitol-negative, trehalose-positive, and all formed an acid curd in litmus milk.

The crucial point in the study of these organisms, however, was their serologic identification. Extracts of each of these three strains of streptococci, prepared by heating acid suspensions in the usual way,[8] reacted with Group N serum prepared by Shattock who first defined Group N, and with a Group N serum recently prepared in this laboratory. These extracts did not react with antisera for streptococcal Groups A, B, C, D, E, F, G, H, L, M and O.* Thus the serologic evidence agreed with the cultural and biochemical methods of identifying the streptococci isolated from the blood stream of this patient with the streptococci from the possible source of infection, both being Strep. lactis and belonging to the serologic Group N.

SUMMARY

A case of subacute bacterial endocarditis caused by Streptococcus lactis is described. An organism similar to that cultured from the blood of the patient was also isolated from a sample of the brand of sour cream which this patient had eaten abundantly prior to his illness. The portal of entry of the Strep. lactis was probably through the irritated gum surrounding a nonvital first lower right molar tooth. This probability is consistent with the findings of Elliott that streptococci serologically identical with those cultured from the gums can be obtained on blood culture following even such mild procedures as slight trauma to the gum or "rocking" a tooth in its socket.[9]

REFERENCES

1. Selbie, F. R., Simon, R. D. and Robinson, R. H. M. Serological classification of viridans streptococci from subacute bacterial endocarditis, teeth, and throats. *Brit. M. J.*, 2: 667, 1949.

* Shattock determined in 1937 that Strep. lactis strains formed a single serologic group, and she designated this group as N in the Lancefield classification. Sherman et al. independently arrived at the same conclusion as to the group specificity of Strep. lactis but did not assign a letter to the group.[5–7]

2. Solowey, M. A serological classification of viridans streptococci with special reference to those isolated from subacute bacterial endocarditis *J. Exper. Med.*, 76: 125, 1942.
3. Okell, C. C. and Elliott, S. D. Bacteriaemia and oral sepsis with special reference to the aetiology of subacute endocarditis. *Lancet*, 2: 869, 1935.
4. Wagner, V. Pathogenicity of Streptococcus lactis. *Schweiz. Ztschr f. Bact. u. Path.*, 7: 163, 1944.
5. Shattock, P. M. F. Thesis, University of Reading, 1937.
6. Sherman, J. M., Smiley, K. C. and Niven, C. F. Serological integrity of S. lactis. *J. Dairy Science*, 23: 529, 1940.
7. Shattock, P. M. F. and Mattick, A. T. R. The serological grouping of S. lactis (Gr. N) and its relationship to S. fecalis. *J. Hyg.*, 43: 173, 1943.
8. Lancefield, R. C. A serological differentiation of human and other groups of hemolytic streptococci. *J. Exper. Med.*, 57: 571, 1933.
9. Elliott, S. D. Bacteriaemia and oral sepsis. *Proc. Roy. Soc. Med.*, 32: 747, 1939.

Quinidine-induced Ventricular Flutter Successfully Treated with Procaine Amide*

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PROCAINE amide is used to restore normal rhythm in various ventricular arrhythmias[1] but we could not find mention of cases of ventricular flutter treated with this drug in the literature. A case of quinidine-induced ventricular flutter treated successfully with intravenous pronestyl® is reported herein.

In a series of fifty patients with chronic atrial fibrillation of rheumatic or arteriosclerotic etiology treated with quinidine we encountered the complication of ventricular flutter twice, a remarkable fact in view of the rarity of this condition. Both patients suffered from inactive rheumatic heart disease.

CASE REPORTS

CASE 1. Mrs. R. R., a fifty-four year old woman, was admitted to the hospital on October 27, 1953, because of dyspnea, weakness and palpitation of one month's duration. The patient had been aware of heart disease for the past twenty years but had had no symptoms referable to it.

Examination revealed a dyspneic, obese woman with distention of the neck veins and slight sacral edema. The liver was enlarged 3 cm. below the right costal margin. Few moist crepitations were heard at both lung bases. At the apex there was a diastolic murmur with marked accentuation of the first sound. At the pulmonary valve area the second sound was accentuated. Atrial fibrillation was present with a ventricular rate of 180 per minute and a pulse deficit of 40.

The laboratory examinations gave normal values for the blood count, increased erythrocyte sedimentation rate, 55/90 (Westergren); total proteins, 6.8 gm. per cent; albumin, 4.0 gm. per cent; globulin, 2.8 gm. per cent; blood urea, 45 mg. per cent. The urine contained 1+ protein, few erythrocytes and leukocytes.

Because of the rapid fibrillation with signs of heart failure the patient was first started on digoxin. The edema disappeared and she was fibrillating at a slower ventricular rate of 72 per minute. Since the heart failure was apparently precipitated by the rapid fibrillation we believed it wise to revert the fibrillation to normal sinus rhythm with quinidine.[2–6] The patient was given dicumarol for two weeks, the prothrombin time being kept between 15 and 20 per cent of the normal. At the same time and during the subsequent quinidine treatment she received maintenance doses of 0.25 to 0.5 mg. of digoxin daily. On December 2, 1953, quinidine treatment was started, first with 0.2 gm. twice daily; later this dose was increased daily by 0.2 gm. until she received 0.2 gm. six times a day. Subsequently every dose was increased by 0.1 gm., so that on the tenth day of treatment she received 0.6 gm. of quinidine six times a day. On the morning of the eleventh day of quinidine therapy, December 11, 1953, sinus rhythm returned and the patient felt much better. In the evening of the same day she suddenly fainted. The examining physician found a heart rate of 100 per minute and the electrocardiogram showed normal sinus rhythm. Her condition improved but shortly afterwards she fainted again, was pale, drenched in a cold perspiration and on regaining consciousness complained of retrosternal oppression. At that time, 7:25 P.M., no pulse was felt and the blood pressure could not be obtained. The electrocardiogram was now typical of ventricular flutter. (Fig. 1.)

Because of the grave prognosis and in spite of the shock we decided to treat her with procaine amide. At 7:30 P.M. intravenous injection of pronestyl® was started at the rate of 100 mg. per minute under continuous electrocardiographic control. After the patient received 2.0 gm., at 7:50 P.M., idioventricular rhythm appeared

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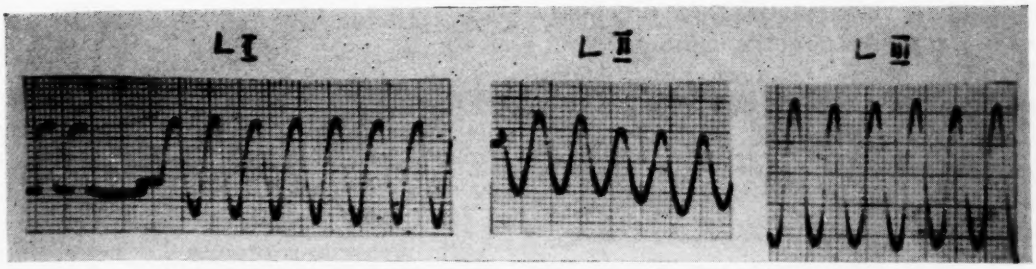

FIG. 1. Case R. R. Three standard leads, showing ventricular flutter.

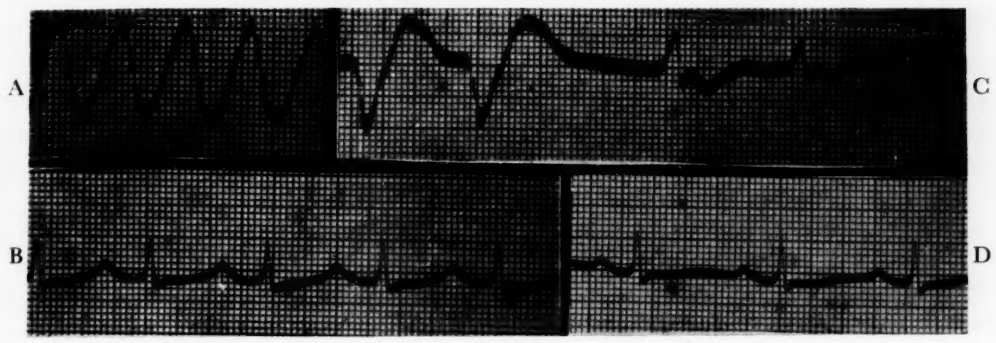

FIG. 2. Case R. R. Restoration of idioventricular rhythm with pronestyl. Lead II: A, 7:36 P.M.; B, 8:02 P.M.; C, 8:15 P.M.; D, 10 P.M.

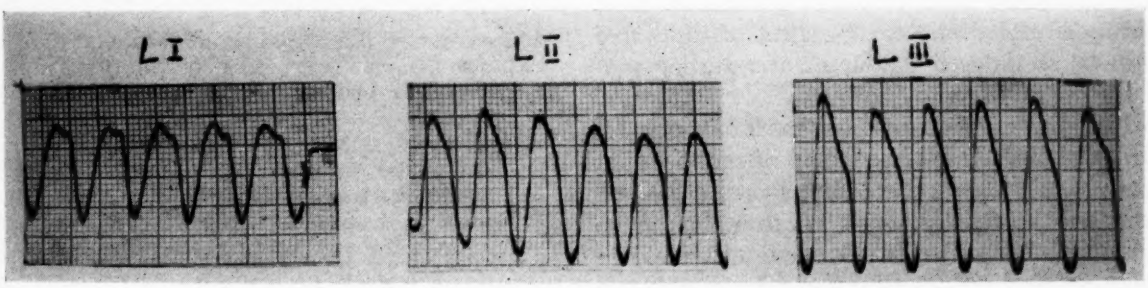

FIG. 3. Case J. Sk. Three standard leads, showing ventricular flutter.

(Fig. 2) and we discontinued the pronestyl injection. The patient felt better, complained only of weakness and nausea, and vomited. The blood pressure rose to 85/70 mm. Hg and later to 95/80. During the subsequent hours the weakness remained, she was unable to void and catheterization of the bladder was necessary. Rapid horizontal nystagmus in both directions was noted. The blood pressure was 110/80. The heart rate was 74 per minute and regular, the pulse was full and the electrocardiogram showed normal sinus rhythm. (Fig. 2, last tracing.) During the following twelve hours she received 0.5 gm. of pronestyl by mouth every four hours and later all treatment was ceased.

The sinus rhythm persisted until December 17th. On this day atrial fibrillation reappeared with ventricular rate of 187 per minute. She now received digoxin and the ventricular rate was slowed. The patient was discharged from the hospital with slow atrial fibrillation and receiving a small maintenance dose of digoxin. There were no signs of heart failure. We saw the patient last on May 17, 1954. She was taking digoxin at home and felt well.

CASE II. Mrs. J. Sk., a forty-two year old woman, was hospitalized elsewhere several times because of chronic heart failure with atrial fibrillation. Prolonged treatment with digitoxin and mersalyl had little effect and it was decided, therefore, to attempt reversal to sinus rhythm. On November 30, 1952, 0.2 gm. of quinidine was given without preliminary dicumarolization. The next day the dose was increased to 0.2 gm. three times a day and during the following period the amount of quinidine administered was increased the same way as in the first case. On the eighth day of treatment the patient suffered two short Adams-Stokes attacks. Electrocardiogram revealed atrial fibrillation with few ventric-

ular premature beats, similar to those previously recorded in this patient. On the night of December 11, 1952, severe cerebral disturbances, delirium, convulsions and tachycardia were noted. The electrocardiogram (Fig. 3) showed ventricular flutter. The patient died shortly afterward.

On postmortem examination signs of congestive heart failure were found, as well as old mitral and tricuspid valvulitis. No emboli were noted in the cerebral vessels.

COMMENTS

Although various cardiac arrhythmias have been frequently described in cases of atrial fibrillation treated with quinidine, we could find only two tracings of ventricular flutter in the literature at our disposal.[3,7,8] The dose of quinidine that the two patients described herein received was not excessively large. The first one received 18.4 gm. and the second one 15.2 gm. in approximately ten days. Both patients received digitalis concurrently with the quinidine. The possibility that digitalis in some way potentiated the toxic action of quinidine must be considered,[8] although the author considers this unlikely.

The first patient received a large dose of pronestyl intravenously in spite of the fact that she was in shock and the blood pressure could not be measured, usually a contraindication to treatment with pronestyl. The good response indicates that pronestyl was of definite value in this case of ventricular flutter.

SUMMARY

1. Two cases of ventricular flutter complicating quinidine treatment of chronic atrial fibrillation are described. Both patients suffered from inactive rheumatic heart disease with signs of congestive heart failure.

2. One of the patients was successfully treated with intravenous pronestyl. The second patient died shortly after the onset of the flutter, before any treatment could be instituted.

REFERENCES

1. Kayden, H. J., Steele, J. M., Mark, L. C. and Brodie, B. B. The use of procaine-amide in cardiac arrhythmias. *Circulation*, 4: 13, 1951.
2. Phillips, E. and Levin, S. A. Auricular fibrillation without other evidence of heart disease. *Am. J. Med.*, 7: 478, 1949.
3. Kartun, P., Azerad, E. and Grupper, C. Le traitement de la fibrillation auriculaire par la quinidine. *Ann. Méd.* 53: 45, 1952.
4. Jount, E., Rosenblum, M. and McMillan, R. L. Treatment of chronic auricular fibrillation. *Arch. Int. Med.*, 89: 63, 1952.
5. Bronstet, P. La fibrillation auriculaire et sa réduction. *Semaine d. hôp., Paris*, 30: 629, 1954.
6. Bedard, O. Quinidine in the treatment of auricular fibrillation. *Am. J. M. Sc.*, 227: 530, 1954.
7. Robertson, E. S. and Matthews, E. C. Paroxysmal ventricular fibrillation producing Adams-Stokes syndrome. *Arch. Int. Med.*, 90: 320, 1952.
8. Binder, M. J. and Rosove, L. Paroxysmal ventricular tachycardia and fibrillation due to quinidine. *Am. J. Med.*, 12: 491, 1952.
9. Gold, H. Quinidine in Disorders of the Heart. New York, 1950. Paul B. Hoeber, Inc.